RESEARCH ARTICLE

Efficacy and Tolerability of Adjuvant Oral Capecitabine plus Intravenous Oxaliplatin (XELOX) in Asian Patients with Colorectal Cancer: 4-Year Analysis

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Abstract

Background: Although FOLFOX (infusional fluorouracil/leucovorin plus oxaliplatin) is established as a standard chemotherapeutic regimen, the long term efficacy of adjuvant XELOX (oral capecitabine plus intravenous oxaliplatin) in Asian colorectal cancer (CRC) patients remains anecdotal. Moreover, uncertainties persist as to whether pharmacogenetic differences in Asian populations preclude equally tolerable and effective administration of these drugs. Method: One hundred consecutive patients with resected colorectal cancer received adjuvant XELOX (oxaliplatin 130 mg/m^2 on day 1 plus capecitabine 900 mg/m^2 twice daily on day 1 to 14 every 3 weeks for 8 cycles) at Queen Mary Hospital, Hong Kong. Endpoints monitored during follow-up were disease-free survival (DFS) and disease recurrence, overall survival (OS) and adverse events (AEs). Results: The median patient age was 56 years, 56% were diagnosed with rectal cancer and 44% with colonic cancer. After a median follow-up of 4.3 years (95% confidence interval, 3.2-4.7), 24 recurrences were confirmed including 13 patients who died due to progressive disease. Four-year DFS was 81% in colon cancer patients and 67% in rectal cancer patients (p=0.06 by log-rank test). For the cohort as a whole, OS was 90% at 3 years and 84% at 5 years. Treatment-related AEs led to early withdrawal in four patients. The commonest non-hematological AEs were neuropathy (91%), hand-foot syndrome (49%) and diarrhea (46%), while the commonest grade 3/4 AEs were neutropenia (11%) and diarrhea (10%). Conclusion: These results confirm the favourable long term survival benefit with good tolerability in using adjuvant XELOX in treating East Asian colorectal cancer patients.

Keywords: Colorectal cancer - adjuvant chemotherapy - XELOX - capecitabine - 5-fluorouracil

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Introduction

Colorectal cancer (CRC) is amongst the top commonly diagnosed cancer in both men and women. The lifetime risk is estimated to be about 1 in 20. With the increased disease awareness in the general public and a variety of easily accessible screening modalities leading to earlier diagnosis, the mortality rate has been decreasing in the last 20 years.

The decrease in mortality is also contributed by the use of adjuvant chemotherapy. The survival benefit of oxaliplatin-based chemotherapy in stage III colon cancer has been well proven in 2 large clinical trials. In both the MOSAIC study evaluating the infusional 5-fluorouracil/leucovorin (5FU/LV) plus oxaliplatin (FOLFOX) and the NSABP C-07 study evaluating bolus 5FU/LV plus oxaliplatin (FLOX), the addition of oxaliplatin significantly prolonged disease free survival (DFS) compared with 5FU/LV alone, with reduction in the risk of recurrence between 21-23% (Andre et al., 2009; Yothers et al., 2011).

Capecitabine (Xeloda®; Hoffmann-La Roche) is an oral pro-drug which can be converted to the active fluropyrimidine by the enzyme thymidine phosphorylase in the tumor tissue. It was shown to be at least as effective as bolus 5FU/LV in the X-ACT study, in which Dukes C colon cancer patients were given adjuvant monochemotherapy 5FU/LV or capecitabine (Reddy, 2004). The concept of substituting 5FU/LV with oral capecitabine was further carried forward in the NO16968 (XELOXA) trial (Haller et al., 2011). In this phase III trial, 1864 patients with resected stage III colon cancer were randomized to receive either XELOX (intravenous oxaliplatin plus oral capecitabine, 3-week cycle for eight cycles) or bolus 5FU/LV (Mayo Clinic regimen). Similar to the MOSAIC trial and the NSABP C-07 trial, it demonstrated a superior 3-year DFS in the XELOX group (70.9% versus 66.5%; hazard ratio [HR] for DFS = 0.8;

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p=0.0045). Notably, the XELOX group experienced less grade 3 to 4 diarrhea, febrile neutropenia, and stomatitis, but more thrombocytopenia, vomiting, and neurosensory toxicity. Although there is no direct comparison between XELOX and FOLFOX, XELOX is in general a well-accepted choice of adjuvant chemotherapy for stage III colon cancer.

Toxicity profile is an important factor for treatment compliance. Ethnic diversity in toxicity profile of capecitabine and metabolism of 5FU has been reported (Wei et al., 1998; Raida et al., 2001; Celik et al., 2002; McCollum et al., 2002; Law et al., 2007). Haller et al. demonstrated in a retrospective analysis that patients from the United States (US) experienced different adverse events and treatment disturbance compared with non-US patients (Haller et al., 2008). As most studies were conducted in Western countries, there is still a paucity of data regarding the toxicity profile of the XELOX regimen in individual ethnic group. CRC is emerging as one of the commonest encountered cancers in many Asian countries. We aimed to explore the long term outcomes of the use of adjuvant XELOX in an Asian colorectal cancer patient cohort.

Materials and Methods

Patients

Consecutive patients with resected colorectal cancer who received XELOX as adjuvant therapy from January 2005 to May 2012 from the Medical Oncology Unit of Queen Mary Hospital, Hong Kong were included in the analysis. All eligible patients were ≥18 years old, had histologically confirmed high-risk stage II or stage III adenocarcinoma of colon or upper/mid rectum (Dukes stage C), and with clear resection margins. Pre-operative whole body imaging, either PET-CT or CAT scan, were performed to exclude distant metastasis. Patients with upper/mid rectal cancer received total mesorectal excision (TME) alone without neoadjuvant treatment according to our unit guideline. All patients had Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2, adequate bone marrow reserve (white blood cell $\geq 3\times10^9$/l, ANC $\geq 1.5\times10^9$/l, and platelet count $\geq 100\times0^9$/l), normal hepatic and renal function. Upon commencement of chemotherapy, patients were fully recovered after curative resection within 6 weeks or within 10 weeks if staged closing ileostomy was required. Patients were excluded from receiving the XELOX treatment if they had known peripheral neuropathy, moderate/severe renal impairment, pregnancy or in lactation.

Treatment and Dose Modification

Patients were treated with XELOX, which consisted of a 2-hour intravenous infusion of oxaliplatin 130 mg/m^2 on day 1, followed by oral capecitabine 900 mg/m^2 twice daily on day 1 to 14 on a 3-week cycle for 8 cycles. Dose modification included delays, dose reduction or interruptions. When grade 2/3 neuropathy developed and lasted longer than 7 days, the dose of oxaliplatin was reduced to 100 mg/m^2, and it was withheld in case of persistent grade 3 or grade 4 neuropathy, allowing capecitabine monotherapy for the rest of the cycles. When grade 2/3 thrombocytopenia developed, both the doses of oxaliplatin and capecitabine were reduced to 100 mg/m^2 and 720 mg/m^2 respectively. When grade 2/3 diarrhea or grade 2/3 hand-foot-syndrome developed, the dose of capecitabine was reduced to 720 mg/m^2.

Baseline Assessment

Demographic data, medical history, concomitant disease and treatment, prior cancer, and family history of cancer, physical examination, hematology and blood chemotherapy including renal and hepatic function, carcinoembryonic antigen (CEA) level and hepatitis B status were assessed one week prior to chemotherapy. Patients were given empirical pre-emptive anti-viral medication if they were hepatitis B carriers.

Follow-up and Disease Evaluation

Patients were followed up every three weeks during treatment, with blood test and adverse events (AEs) evaluated. In the first 2 years after completion of treatment, they were followed up every 3 months for checking of CEA and physical examination. Surveillance imaging by PET-CT or CAT scan was done every year for 3 years. Surveillance colonoscopy was done within 1 year if it was done before surgery or within 3 to 6 months if a full colonoscopy was not done before surgery, then every 3 years if normal. Thereafter patients were followed up every 6 months if all investigations were normal. DFS was defined as the time between commencement of chemotherapy and tumor recurrence, the occurrence of a new primary colon cancer, death from any cause, or the last date at which the patient was known to be disease-free. Overall survival was defined as the time from commencement to death from any cause or the date at which the patient was last confirmed to be alive.

AEs were monitored continuously during treatment and for 8 weeks after last completion of treatment. They were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

Statistical Analysis

Demographic and clinical data was analyzed as categorical variables. Safety parameters included AEs, laboratory parameters, and number of cycles at which grade 3/4 toxicities developed. Dose intensity was calculated as followed: total dose given/planned total dose. Safety parameters were further compared between subgroup of patients with colon or rectal cancer. DFS and OS were analysed by Kaplan-Meier estimates and compared using log-rank test. Frequency of adverse events were analysed by Fisher's exact test. A p-value of ≤ 0.05 was considered statistically significant.

Results

Demographics

This study included 100 consecutive CRC patients who received XELOX as adjuvant treatment for patients with early CRC during the study period. Their demographic and

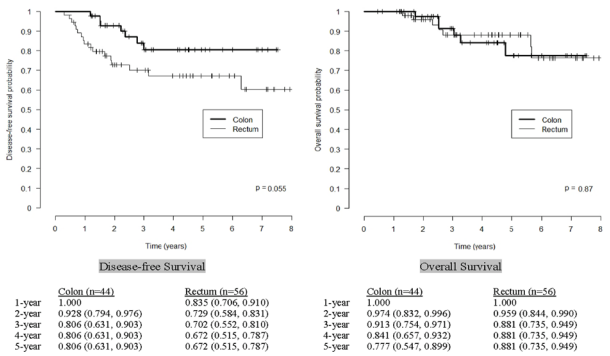
Table 1. Baseline Characteristics

Characteristics	All	Colon[a] (n=44)	Rectum[b] (n=56)	*p*-value
Age (years)				
Median (range)	55.59 (28.21-80.14)	54.22 (28.21, 76.06)	55.72 (32.15, 80.14)	0.838
Sex				
Male	56 (56%)	25 (56.82%)	31 (55.36%)	1
Female	44 (44%)	19 (43.18%)	25 (44.64%)	
ECOG performance status				
0	88 (88%)	36 (81.82%)	52 (92.86%)	0.124
1	12 (12%)	8 (18.18%)	4 (7.14%)	
N staging				
N0	2 (2%)	1 (2.27%)	1 (1.79%)	0.031
N1	53 (53%)	30 (68.18%)	23 (41.07%)	
N2a	27 (27%)	7 (15.91%)	20 (35.71%)	
N2b	18 (18%)	6 (13.64%)	12 (21.43%)	
Histologic appearance				
Well differentiated	3 (3%)	0 (0.00%)	3 (5.36%)	0.047
Moderately differentiated	85 (85%)	40 (90.91%)	45 (80.36%)	
Poorly differentiated	8 (8%)	1 (2.27%)	7 (12.50%)	
missing	4 (4%)	3 (6.82%)	1 (1.79%)	
Lymphovascular invasion				
No	28 (16%)	13 (29.55%)	15 (26.79%)	0.649
Yes	56 (56%)	23 (52.27%)	33 (58.93%)	
missing	16 (16%)	8 (18.18%)	8 (14.29%)	
Comorbidity				
Cardiovascular	21 (21%)	5 (11.36%)	16 (28.57%)	0.048
DM	5 (5%)	1 (2.27%)	4 (7.14%)	0.381
Cardiovascular/DM	22 (22%)	6 (13.64%)	16 (28.57%)	0.091
Hyperlipidemia	10 (10%)	4 (9.0%)	6 (10.71%)	1

DM, Diabetes mellitus; [a]"Colon" includes colon, caecum, sigmoid; [b]"Rectum" includes rectosigmoid, rectum

Table 2. Details of Recurrence Cases

	n = 24
Cue to recurrence	
CEA rise	6 (25.00%)
CT / PET-CT	14 (58.33%)
Physical exam	3 (12.50%)
Per rectal bleeding	1 (4.17%)
Site of recurrence	
Distant	21 (87.50%)
Local only	3 (12.50%)
K-Ras status	
Wild type	12 (50.00%)
Mutant	7 (29.17%)
Unknown	5 (20.83%)



	Colon (n=44)	Rectum (n=56)
1-year	1.000	0.835 (0.706, 0.910)
2-year	0.928 (0.794, 0.976)	0.729 (0.584, 0.831)
3-year	0.806 (0.631, 0.903)	0.702 (0.552, 0.810)
4-year	0.806 (0.631, 0.903)	0.672 (0.515, 0.787)
5-year	0.806 (0.631, 0.903)	0.672 (0.515, 0.787)

	Colon (n=44)	Rectum (n=56)
1-year	1.000	1.000
2-year	0.974 (0.832, 0.996)	0.959 (0.844, 0.990)
3-year	0.913 (0.754, 0.971)	0.881 (0.735, 0.949)
4-year	0.841 (0.657, 0.932)	0.881 (0.735, 0.949)
5-year	0.777 (0.547, 0.899)	0.881 (0.735, 0.949)

Figure 1. Kaplan-Meier Estimate of Disease-free Survival and Overall Survival with 95% Confidence Intervals

clinical characteristics are shown in Table 1. The histologic appearance and N staging were different between the colon cancer and the rectal cancer patients. Worth noting, patients with rectal cancer had more N2 disease (57.1% vs. 29.5%, p=0.008). The clinical characteristics were otherwise similar between these two groups. The median time from surgery to commencement of chemotherapy was 5.29 weeks and the follow up time was 4.31 years (95% confidence interval [C.I.], 3.24, 4.65).

Disease-free Survival and Overall Survival

At time of analysis, 24 patients had disease recurrence (24%), of which 17 were rectal cancer patients (p=0.105). The median time-to-recurrence was 1.39 years (0.29-6.28 years). The majority was detected by surveillance imaging (58.3%), and 25% presented as elevated CEA, and 12.5% presented with symptoms or abnormal physical examination (Table 2). Distant metastasis was found in 87.5% and the rest had local recurrence only. There was more recurrence in rectal cancer patients (30.36% vs 15.91%) but it did not reach statistical significance (p=0.105). There were 13 deaths, 6 were colon and 7 were rectal cancer patients (p=1.000), and all were due to progressive disease. The 4-year DFS rate was 80.6% for colon cancer and 67.2% for rectal cancer (p=0.055). The overall OS at 3-year and at 5-year were 89.6% (95% C.I., 80.2%, 94.7%) and 83.8% (95% C.I., 71.9%, 90.9%), respectively. There was no difference between two groups. Kaplan-Meier estimates of DFS and OS of the 2 groups are shown in Figure 1.

Tolerability, Safety and Dose Intensity

Treatment related AEs are shown in Table 3 and 4. The most common non-hematological AEs were neuropathy (91%) with the majority having grade 1 severity, followed by hand-foot syndrome (49%). Diarrhea was reported in 46% of patients and 10% were grade 3 symptoms. Haematological AEs were also commonly encountered. Anemia, all of which grade 1-2, was found in 84% of

Table 3. Most Common Treatment-related Adverse Events

Adverse event	No. (%)	Colon (n=44)	Rectum (n=56)	*p*-value[c]
Diarrhea	46 (46%)	G1 - 12 / G2 - 3 / G3 - 3	G1 - 17 / G2 - 4 / G3 - 7	0.422
Hand-foot syndrome	49 (49%)	G1 - 17 / G2 - 5 / G3 - 0	G1 - 22 / G2 - 4 / G3 - 1	1.000
Neuropathy	91 (91%)	G1 - 40 / G2 - 1 / G3 - 0	G1 - 45 / G2 - 5 / G3 - 0	0.727
Vomiting	7 (7%)	G1 - 2 / G2 - 1 / G3 - 0	G1 - 2 / G2 - 0 / G3 - 2	1.000
Nausea	15 (15%)	G1 - 8 / G2 - 0 / G3 - 1	G1 - 6 / G2 - 0 / G3 - 0	0.259
Malaise	15 (15%)	G1 - 6 / G2 - 1 / G3 - 0	G1 - 7 / G2 - 1 / G3 - 0	1.000
Stomatitis	5 (5%)	G1 - 1 / G2 - 1 / G3 - 0	G1 - 3 / G2 - 0 / G3 - 0	1.000
Neutropenia	67 (67%)	G1 - 19 / G2 - 13 / G3 - 3	G1 - 13 / G2 - 11 / G3 - 8	0.020
Thrombocytopenia	84 (84%)	G1 - 30 / G2 - 6 / G3 - 5	G1 - 32 / G2 - 7 / G3 - 4	0.030
Anaemia	84 (84%)	G1 - 35 / G2 - 3 / G3 - 0	G1 - 43 / G2 - 3 / G3 - 0	0.597
Leukopenia	54 (54%)	G1 - 19 / G2 - 7 / G3 - 0	G1 - 16 / G2 - 12 / G3 - 0	0.422

[c]p-value from Fisher's exact test for comparison of presence of the AE (any grade)

Table 4. Most Common Grade 3/4 Treatment-related Adverse Events

Adverse event	No.(%)	Colon(n=44)	Rectum(n=56)	*p*-value
Neutropenia	11 (11%)	3 (6.82%)	8 (14.29%)	0.338
Diarrhea	10 (10%)	3 (6.82%)	7 (12.50%)	0.506
Thrombocytopenia	9 (9%)	5 (11.36%)	4 (7.14%)	0.501

Table 5. Dose Intensity, Treatment Modifications and Withdrawals

Parameter	Overall	Colon (n=44)	Rectum (n=56)	*p*-value
Median dose intensity				
Oxaliplatin	100%	100%	100%	0.567
Capecitabine	100%	100%	100%	0.580
Number of cycles				
< 8	7 (7%)	3 (6.82%)	4 (7.14%)	1.000
8	93 (93%)	41 (93.18%)	52 (92.86%)	
Toxicity-related withdrawal	4 (4%)	3 (6.82%)	1 (1.79%)	0.317
Treatment modification				
a. ≥ 1 dose reduction	45 (45%)	20 (45.45%)	25 (44.64%)	1.000
Oxaliplatin	39	18	21	0.837
Capecitabine	39	15	24	0.414
b. ≥ 1 cycle interruption	38 (38%)	17 (38.64%)	21 (37.50%)	1.000

Table 6. Comparison of Most Common Treatment-related AEs and Survival with Previous Studies

	Current study	Haller's paper	
		US	East Asia
No. of patients	100	180	100
Adverse events			
Any adverse events	100%	100%	98%
Grade 3/4 adverse events	28%	68%	43%
Grade 3/4 gastrointestinal symptoms	13% (10% diarrhea)	37%	8%
Grade 3/4 hand-foot syndrome	1%	11%	1%
Grade 3/4 neutropenia	11%	8%	23%
Grade 3/4 thrombocytopenia	9%	Not available	Not available
Survival (colon cancer)			
4 year disease-free survival	80.6%	69.7%	
5 year overall survival	77.7%	77.6%	

patients. Thrombocytopenia was found in 84% of patients and 9% of patients had grade 3 symptom. Neutropenia was found in 67% of patients and 11% had grade 3 symptom. Table 5 summarizes the pattern of dose intensity and treatment modifications. There was no difference between both groups. The median dose intensities for both oxaliplatin and capecitabine were 100%, and 93% of patients completed all 8 cycles. Among the seven patients who did not complete treatment, four withdrew due to neutropenia, two was lost to follow up, and one developed recurrence during treatment. Forty-five percent of patients required at least 1 dose reduction. The main AEs leading to dose reduction were thrombocytopenia, diarrhea, neutropenia (18, 11, and 8 patients respectively). Thirty-five percent of patients had cycle interruption due to AEs.

Discussion

This study is the first to assess the safety and efficacy of XELOX in a non-Westerner population, namely ethnic Chinese. The central finding is that XELOX regimen was generally tolerated well in this population, with comparable survival parameters to counterpart studies (Table 6). More importantly, our study provides preliminary survival data to support the efficacy of XELOX in the adjuvant setting. There are two published trials showing a favourable survival outcome and tolerability associated with the use of XELOX in the adjuvant setting (Schmoll et al., 2007; Haller et al., 2011). However, our study contained a wider range of standard (non-trial) patients than in controlled clinical studies, thus better representing the reality of everyday clinical practice.

The combination of oxaliplatin plus 5FU remains a standard choice of adjuvant chemotherapy in colorectal cancer, notwithstanding that physicians increasingly choose XELOX instead of the infusional regimen nowadays due to convenience (de Gramont et al., 2011). Although the survival data of adjuvant XELOX is only available in the literature in recent few years, our center has adopted this regimen as adjuvant therapy for colorectal cancer early. It was based on the results from the adjuvant X-ACT study where capecitabine was non-inferior to infusional 5-FU (Reddy, 2004), and studies for metastatic colon cancer where XELOX was found to have similar efficacy with FOLFOX4 (Teitelbaum and Haller, 2009). Moreover, pharmacoeconomic data comparing XELOX and FOLFOX4 showed that XELOX was more cost-effective, and was associated with better adherence to treatment, better likelihood of completion of treatment and improved quality of life (Tse et al., 2011).

According to the guideline issued by the Department of Health and Human Services in the US (Ref), ethnic factors could be the cause for potential regional differences in drug effects, and these issues should be addressed in the process of global drug development. Regional differences have important implication in both the regulatory process and clinical practice, and should be considered in early clinical trials, and be part of a continuous evaluation program after the drug or regimen is approved. Most large clinical trials on which drug approval by major international regulatory bodies based are conducted in Western countries. With the advances in understanding of pharmacogenomic of drugs, and ethnic differences in tumor biology, it becomes clear that the results of these large clinical trials might not be extrapolated directly to other regions of the world. Haller et al. had published their retrospective analysis of two phase III clinical studies on capecitabine versus IV 5FU/LV for metastatic colorectal cancer and a phase III trial comparing XELOX with IV 5FU/LV, to explore the differences in AEs in response to fluoropyrimidines between US and non-US patients (Haller et al., 2008). They also did a subgroup analysis to compare the more severe AEs between US and East Asian patients. Table 6 showed that our results were consistent with their findings that East Asians were clearly less susceptible to severe gastrointestinal (GI) symptom (current study, East Asian patients, US patients - 13%, 8%, 37%) and hand-foot syndrome (1%, 1%, 11%). These are major AEs that caused treatment disruption, dose modification and treatment withdrawal. Nevertheless, the frequency of grade 3 to 4 neutropenia in the East Asian group in Haller's study was much higher than our study (11% vs 23%). It might partially be explained by the differences in the dosage of capecitabine adopted in

these studies. Most Western studies used a capecitabine dosage of 1000-1250 mg/m^2 twice per day from day 1 to 14 every 3 weeks. Our protocol chose a lower dose of 900 mg/m^2 for the same dosing frequency. This 10-20% reduction in the dose could result in less haematological toxicities. Despite better neutrophil profile in our study, there was a 9% rate of grade 3-4 thrombocytopenia in our study and it accounted for an important reason for subsequent dosage modification. The rate of severe thrombocytopenia in the XELOXA trial was 5%, its differential rates among different ethnic groups were not reported in Haller's retrospective study. Therefore we cannot determine if Chinese were more susceptible to this marrow toxicity compared with their Western counterpart. Our survival data were at least as good as those of the counterpart studies, and there was no evidence to suggest starting capecitabine at this lower dose could compromise treatment efficacy. In fact there is no consensus on standard dosage of capecitabine, and the choice is often subjected to discretion of clinical experience and local practice. Many factors can influence the perceived toxicities of this drug. There can be intrinsic factors, namely gender, age, body built, genetic elements, physiological status, and organ functions, as well as extrinsic factors, such as climate, socioeconomic, education status, diet, medical practice and trial methodology and reporting (Teitelbaum and Haller, 2009). The collective findings of Haller's and our studies suggested East Asians and Chinese tolerate capecitabine better in general and it should be a favourable consideration in the development of capecitabine-containing chemotherapy regime.

Our patient group contained colon as well as patients with upper or mid rectal tumour. Adjuvant therapy in resected these groups of rectal cancer patients has been a controversial topic. All our patients with upper or mid rectal cancer received total mesorectal excision(TME) without peri-operative radiotherapy due to practicing policy of our unit. TME is a surgical technique well recognized to reduce local recurrence (McCall et al., 1995). Addition of radiotherapy to TME appeared to improve local control but not OS (Kapiteijn et al., 2001), yet the optimal mode of radiotherapy (RT) has not been well defined by phase III trial. Although it is a common practice to offer pre-operative chemoradiotherpy (CRT) to T3 or node positive disease, use of combination CRT with infusional 5-FU is based on the Intergroup study 8647451 (O'Connell et al., 1994), which was started in the 80's and it showed addition of chemotherapy to RT reduced overall time to distant relapse (p=0.01) and improved survival (p=0.005), but not affect local recurrence. These results suggest the survival benefit of CRT mainly derived from chemotherapy. Six months of adjuvant FOLFOX has been well proven to improve survival compared with 5FU alone in high-risk stage II and stage III colon cancer (Andre et al., 2009; Yothers et al., 2011). Due to this promising result, many oncologists advocate the use of this regimen as adjuvant treatment in rectal cancer, especially when it involves only upper and mid rectum.

The major limitation of the current study is due to its retrospective in nature with a relatively small number of patients. Nevertheless, our study had a wider range of patients compared with the stringent and highly controlled criteria in clinical studies, thus it might better represent the situation in the real life practice. Moreover, we have a relatively long follow up period with the median follow-up time in this study being 4.31 years. Notably, 3-year DFS is a strong predictor of OS for 5FU-containing combination chemotherapy (Sargent et al., 2007) and it is agreed by various regulatory authorities to be adopted as the candidate for primary end point for adjuvant cancer trials. Therefore, we believe our data are mature enough to shed light in this important topic.

In conclusion, XELOX is tolerated well in ethnic Chinese with comparable historical survival efficacy. There were no severe skin or GI symptoms, as have commonly been observed in Westerners, suggesting at least equivalent efficacy. Based on these data, we submit that XELOX can now be considered a standard adjuvant treatment option for East Asian colorectal cancer patients.

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