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Original Article

The efficacy of XELOX and FOLFOX adjuvant chemotherapy in stage III colorectal cancer patients with low preoperative serum albumin levels

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Abstract: The incidence of advanced stage colorectal cancer (CRC) patients is increasing. Adjuvant chemotherapy [5-fluorouracil/leucovorin plus oxaliplatin (FOLOX) or capecitabine plus oxaliplatin (XELOX) is the standard treatment for patients with stage III CRC following surgery, with the objective of avoiding tumor recurrence and metastasis. However, the selection of an optimal treatment regimen is still necessary when managing elderly CRC patients. Seventy-five CRC elderly patients (aged ≥ 60 years) with stage III CRC who presented at the cancer center of Changhua Show Chwan Memorial Hospital from 2007-2014 were enrolled in this study. Sixty patients received FOLFOX and XELOX adjuvant chemotherapy. The remaining 15 did not. The overall survival (OS) and relapse-free survival (RFS) of the two groups [those who received adjuvant chemotherapy (XELOX and FOLOX) and those who did not] was analyzed using the Kaplan-Meier estimator and the Cox regression method. Longer periods of OS and RFS were found in patients in the FOLFOX or XELOX adjuvant chemotherapy regimen group compared with those in the non-adjuvant chemotherapy group. Five-year survival of 36.8% (OS) and 41.6% (RFS) was reported in the XELOX group and 58.0% (OS) and 90.0% (RFS) in the FOLFOX group, respectively, using the Kaplan-Meier estimator. Following Cox regression, it was revealed that the adjusted hazard ratio relating to non-adjuvant chemotherapy was 0.302 (a range of 0.130-0.703) and 0.437 (a range of 0.202-0.943) for the XELOX, and 0.112 (a range of 0.014-0.913) and 0.124 (a range of 0.015-1.016) for the FOLFOX, adjuvant chemotherapy regimen groups, for OS and RFS, respectively. In addition, CRC patients with low preoperative serum albumin levels (≤ 3.5 g/dl) experienced inferior OS compared to those with high preoperative serum albumin levels (≥ 3.5 g/dl). Better clinical outcomes were found in patients with low preoperative serum albumin levels in the FOLFOX and XELOX adjuvant chemotherapy groups, compared to those with similar levels who did not receive adjuvant chemotherapy. Conversely, preoperative serum albumin levels of ≥ 3.5 g/dl in the elderly was an indication that chemotherapy was not warranted. Thus, it was determined on conclusion of the study that chemotherapy treatment for CRC was only indicated in the elderly when preoperative serum albumin levels of ≥ 3.5 g/dl were recorded.

Keywords: XELOX, FOLFOX, adjuvant chemotherapy and colorectal cancer

Introduction

The highest incidence of cancer in Taiwan pertains to colorectal cancer (CRC), which is also the third leading cause of cancer-related deaths in the country. Nevertheless, the prognosis of patients with CRC is more favorable than that in patients with other cancer types [1]. Generally, surgery is the major curative treatment for colon cancer. This includes wide local excision of tumors and mesocolons. Lymphovascular tissue, recurrence and metastasis are common after surgery. Therefore, postoperative adjuvant chemotherapy is administered to eradicate recurrence or metastasis in patients with stage II (Dukes' B) and stage III (Dukes' C) CRC [2, 3].

In a large-scale meta-analysis, Landre *et al.* (2015) reported that the addition of oxaliplatin

Table 1. Relationships of various clinical parameters and with and without adjuvant chemotherapy (XELOX and FOLFOX) in patients with stage III colorectal cancer

Characteristics	N = 75	Adjuvant chemotherapy			*P*-value
		No	Yes		
		N = 15	XELOX N = 38	FOLFOX N = 22	
Age (y/o) (mean ± SD)	74.0±7.6	79.6±8.6	73.3±6.7	69.2±5.5	0.001
< 65	11	2	7	2	0.875
≥ 65	64	13	43	8	
Gender					
Female	36	12	19	5	0.017
Male	39	3	31	5	
Pathologic staging					
pT1, pT2	5	0	4	1	0.498
pT3, pT4	66	15	4	0	
pN					
pN1	48	8	35	5	0.305
pN2	27	7	15	5	
WBC (mean ± SD)	8063.0±3298.4	8173.3±4520.7	7804.1±2785.6	9288.9±3670.0	0.464
< 10^4/ml	56	11	40	5	0.221
≥ 10^4/ml	17	4	9	4	
Albumin (mean ± SD)	3.4±0.8	2.9±0.9	3.5±0.7	3.5±0.7	0.018
< 3.5 g/dl	33	10	20	3	0.195
≥ 3.5 g/dl	33	4	25	4	
CEA	17.1±35.3	9.2±8.1	20.6±42.5	12.0±14.4	0.496
< 10 ng/ml	48	10	31	7	0.908
≥ 10 ng/ml	26	5	18	3	

P value was obtained from Chi-square test. WBC, white blood cell count; CEA, carcinoembryonic antigen.

or irinotecan to 5-fluorouracil (FU) in metastatic CRC significantly improved relapse-free survival (RFS) in elderly patients aged ≥ 70 years but was associated with an increased risk of toxicity, as shown for irinotecan [4]. Currently, it is well established that FU-based adjuvant chemotherapy regimens, such as uracil/tegafur and 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX), reduce recurrence and prolong survival, especially in stage III, but not in stage II, disease [5]. Furthermore, capecitabine plus oxaliplatin (XELOX) adjuvant chemotherapy significantly was shown to increase disease-free survival (DFS) and overall survival (OS), when compared with bolus leucovorin and fluorouracil in the XELOXA trial [6]. Similarly, it was demonstrated in a study that efficacy outcomes remained the same with capecitabine-, leucovorin-, and FU-based regimens but that post-relapse survival reduced in patients who received adjuvant oxaliplatin [7].

Thus, as the efficacy of FOLFOX and XELOX adjuvant chemotherapy remains elusive in stage III CRC patients compared with those who are not receiving adjuvant chemotherapy, the objective of this study was to evaluate OS and RFS in both groups of patients using the Kaplan-Meier estimator and the Cox regression method.

Methods and materials

Subjects

Seventy-five patients with CRC who had received FOLFOX and XELOX chemotherapy following surgical resection from 2007 to 2014 with clinical parameters and OS data were obtained from the de-identified cancer registry database from Show Chwan Memorial Hospital. All of the patients were unrelated, of ethnic Chinese descent, and were residents in central Taiwan. The TNM Classification of Malignant

Table 2. Univariate analysis of prognostic factors for OS and RFS in stage III colorectal cancer patients

Characteristics	No.	OS		Log-rank	RFS		Log-rank
		Median survival (months)	5-year survival (%)		Median survival (months)	5-year urvival (%)	
Age (y/o)							
< 65	11	29.6	81.8%	0.499	29.6	72.7%	0.555
≥ 65	64	25.3	64.1%		26.7	57.1%	
Gender							
Female	36	34.7	55.6%	0.197	33.3	55.6%	0.850
Male	39	33.3	76.9%		22.2	63.2%	
Pathologic staging							
pT1, pT2	5	18.5	60.0%	0.624	18.5	60.0%	0.797
pT3, pT4	70	34.1	67.1%		29.0	59.4%	
pN							
pN1	48	36.4	68.8%	0.538	32.0	62.5%	0.353
pN2	27	32.4	63.0%		25.0	53.8%	
WBC							
< 10^4/ml	56	34.2	71.4%	0.081	29.3	64.3%	0.053
≥ 10^4/ml	17	24.9	47.1%		17.7	41.2%	
Albumin							
< 3.5 g/dl	33	874	51.5%	0.023	18.5	48.5%	0.101
≥ 3.5 g/dl	33	912	78.8%		29.0	66.7%	
CEA							
< 10 ng/ml	48	32.2	64.6%	0.548	22.4	58.3%	0.630
≥ 10 ng/ml	26	35.7	69.2%		29.6	61.5%	
Adjuvant chemotherapy							
No	15	12.6	26.7%	< 0.001	9.5	26.7%	0.002
XELOX	50	36.8	74.0%		29.0	58.0%	
FOLFOX	10	41.6	90.0%		60.0	90.0%	

Tumor stage and the tumor type and stage of each collected specimen were histologically determined according to the World Health Organization classification system. The age of the patients ranged from 60-92 years [mean ± standard deviation (SD) = 74.0 ± 7.6]. Survival time was defined as the period from the date of the primary surgery to the date of death. Twenty-five patients died during this study and 18 patients were observed to have relapsed, based on the follow-up data.

Statistical analysis

Statistical analysis was conducted using SPSS® version 18. The associations between adjuvant chemotherapy of XELOX and FOLFOX and clinical parameters were analyzed by a x^2-test. Independent t Test was performed for comparison of the age, WBC, albumin, and CEA among the adjuvant chemotherapy styles. Overall survival (OS) and relapse-free survival (RFS) plots were generated using the Kaplan-Meier method, and differences between patient groups were determined by a log-rank test. Five-year survival for the whole test set was estimated using the Kaplan-Meier estimator. Multivariate and univariate Cox regression analysis was conducted to assess the prognostic values Overall survival (OS) and relapse-free survival (RFS). *A p*-value of ≤ 0.050 was considered to be statistically significant.

Results

Correlation between age, gender, and serum albumin levels, and an adjuvant chemotherapy regimen in patients with colorectal cancer

Seventy-five stage III CRC patients were enrolled in the study. Sixty patients received adjuvant chemotherapy and 15 did not. There

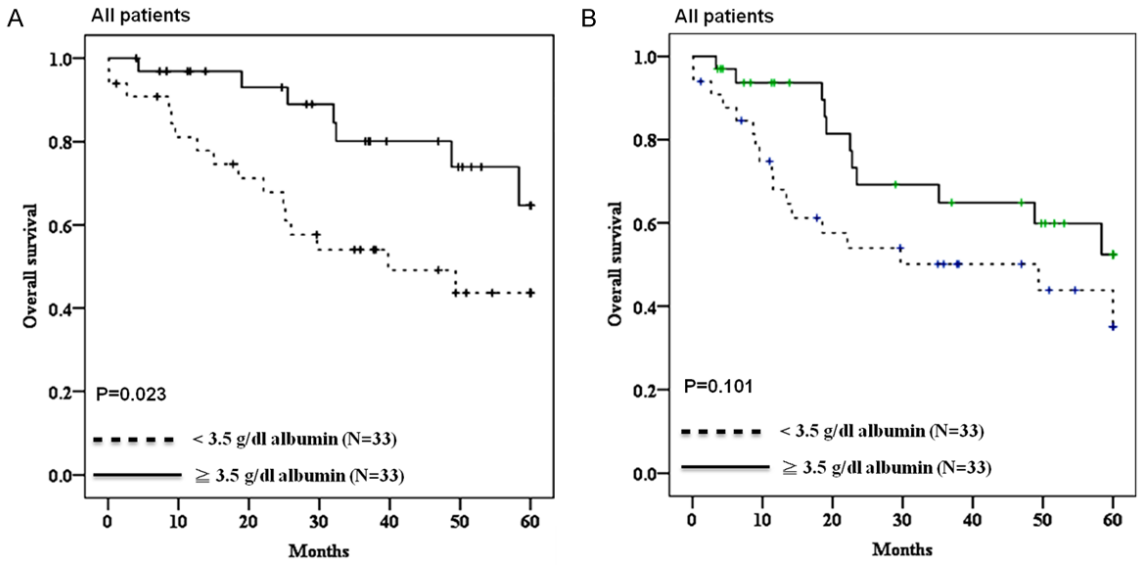

Figure 1. Kaplan-Meier analysis of the influence of serunn albumin level on OS and RFS in CRC patients. A. ≥ 3.5 g/dl albumin or < 3.5 g/dl in CRC patients for OS. B. ≥ 3.5 g/dl albumin or < 3.5 g/dl in patients for RFS.

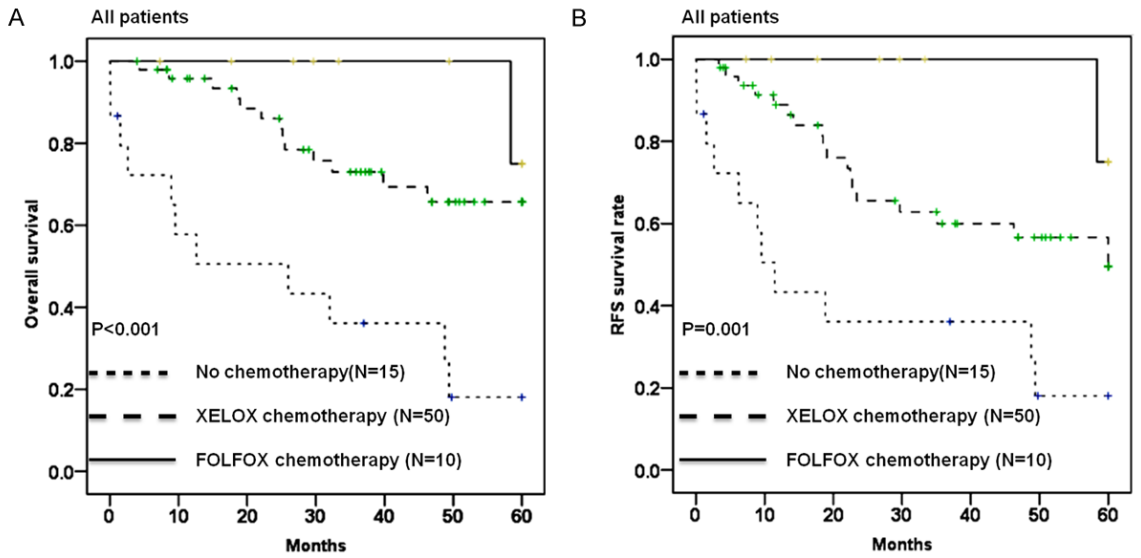

Figure 2. Kaplan-Meier analysis of the influence of adjuvant chemotherapy (XELOX or FOLFOX) on OS and RFS. A. Adjuvant chemotherapy or no chemotherapy in patients for OS. B. Adjuvant chemotherapy or no chemotherapy in patients for OS.

were more males than females in the XELOX and FOLFOX adjuvant chemotherapy groups (P = 0.017) (**Table 1**). The mean age in the adjuvant chemotherapy group was lower than that in the non-adjuvant chemotherapy group (P = 0.001) (**Table 1**). The mean serum albumin level was higher in the adjuvant chemotherapy group than that in the non-adjuvant chemotherapy group (P = 0.018) (**Table 1**). These results demonstrate that patients with CRC received adjuvant chemotherapy based on a prior evaluation of their age, gender, and serum albumin levels.

Adjuvant chemotherapy and elevated serum albumin are associated with favorable overall and relapse-free survival in patients with colorectal cancer

It was further investigated whether or not adjuvant chemotherapy had a positive impact on the OS and RFS of patients with stage III CRC

Table 3. Mutivariate analysis of prognostic factors for OS and RFS in stage III colorectal cancer patients

Characteristics	Favorable/Unfavorable	OS		RFS	
		Multivariate	HR (95% CI)	Multivariate	HR (95% CI)
		P-value		*P*-value	
Albumin	≥ 3.5 g/dl/< 3.5 g/dl	0.043	0.397 (0.163-0.970)	0.156	0.156 (0.575-1.234)
Adjuvant chemotherapy	XELOX/No	0.005	0.302 (0.130-0.703)	0.035	0.437 (0.202-0.943)
	FOLFOX/No	0.041	0.112 (0.014-0.913)	0.052	0.124 (0.015-1.016)

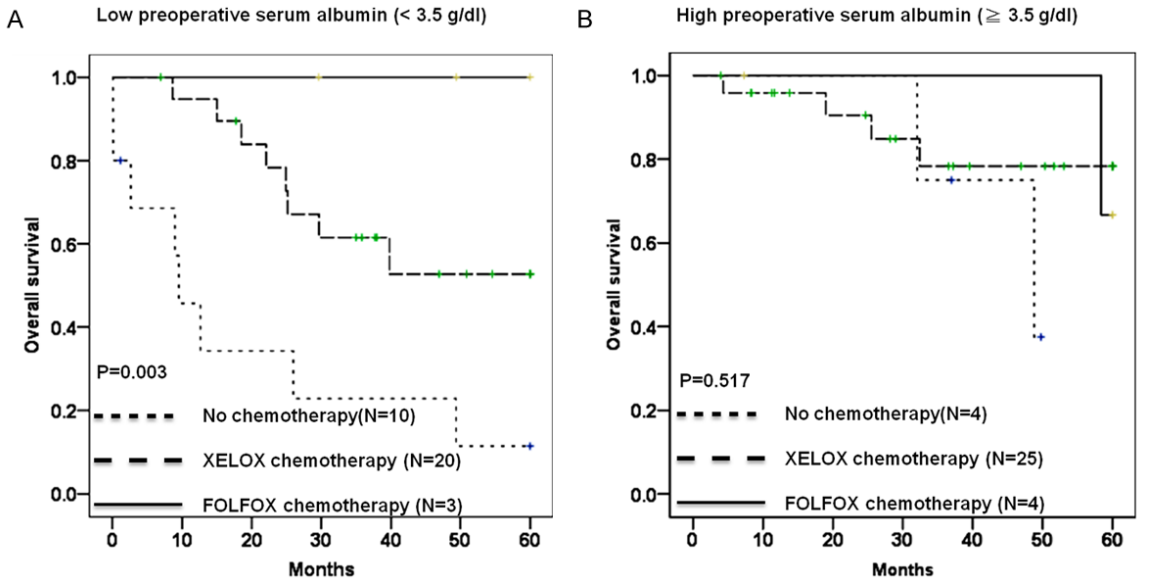

Figure 3. Kaplan-Meier analysis of the influence of adjuvant chemotherapy (XELOX or FOLFOX) in ≥ 3.5 g/dl albumin or < 3.5 g/dl in CRC patients for OS. A. Adjuvant chemotherapy or no chemotherapy in patients for OS in CRC patients who harbored < 3.5 g/dl albuminn. B. Adjuvant chemotherapy or no chemotherapy in patients for OS in\CRC patients who harbored ≥ 3.5 g/dl albuminn.

using the Kaplan-Meier estimator and the Cox regression model. Interestingly, longer OS was observed in patients with CRC with serum albumin levels of ≥ 3.5 g/dl than in those with a serum albumin level ≤ 3.5 g/dl. Five-year survival was 78.7% in those with serum albumin levels ≥ 3.5 g/dl versus 51.5% in those with serum albumin levels ≤ 3.5 g/dl (P = 0.023) (**Table 2** and **Figure 1**).

As expected, patients who received adjuvant chemotherapy experienced longer OS and RFS than those who did not receive it (P = < 0.001 and P = 0.001, respectively) (**Table 2** and **Figure 2**).

Interestingly, it was found that patients in the FOLFOX adjuvant chemotherapy group experienced better five-year survival, in terms of OS and RFS, than those in the XELOX adjuvant chemotherapy group [90.0% versus 74.0% (OS) and 90.0% versus 58.0% (RFS), respectively].

It was also found that patients with serum albumin levels ≥ 3.5 g/dl and who had received adjuvant chemotherapy experienced better five-year OS and RFS.

Following Cox regression analysis, it was found that CRC patients on the XELOX adjuvant chemotherapy regimen had a hazard ratio (HR) of 0.302 and 0.437 for OS and RFS, respectively, compared to CRC patients who were not on it [95% confidence interval (CI): 0.13-0.70, P = 0.005 for OS; 95% CI: 0.20-0.94, P = 0.035 for RFS, respectively] (**Table 3**). Additionally, patients on the FOLFOX adjuvant chemotherapy regimen had a HR of 0.112 and 0.124 for OS and RFS, respectively, compared with CRC patients who were not on it (95% CI: 0.01-0.91,

P = 0.041 for OS; 95% CI: 0.02-1.02, P = 0.052 for RFS, respectively) (**Table 3**).

The positive impact of a ≥ 3.5 g/dl serum albumin level on the HR for OS and RFS was observed when compared to that for CRC patients with similar albumin levels who were not on adjuvant chemotherapy (HR: 0.397, 95% CI: 0.16-0.97 for OS and HR: 0.156, 95% CI: 0.58-1.23 for RFS) (**Table 3**).

Adjuvant chemotherapy improved overall and relapse-free survival in CRC patients with a low preoperative serum albumin level

The benefit of adjuvant chemotherapy, independent of or dependent on preoperative serum albumin levels in stage III CRC patients, was also investigated. Therefore, the patients were stratified into two groups (≤ 3.5 g/dl and ≥ 3.5 g/dl). The benefit of adjuvant chemotherapy in patients with stage III CRC was observed in the ≥ 3.5 g/dl group (*P* = 0.003) (**Figure 3**) and not in the ≤ 3.5 g/dl group (*P* = 0.517) (**Figure 3**). These findings demonstrate that adjuvant chemotherapy could promote survival in patients with stage III CRC with low preoperative albumin serum levels.

Discussion

In the current study, stage III CRC patients with serum albumin levels of ≥ 3.5 g/dl and who had received adjuvant chemotherapy experienced longer periods of OS and RFS than those who did not receive it and who had serum albumin levels of ≤ 3.5 g/dl. In addition, survival was significantly higher in patients aged ≥ 65 years with stage III CRC, who were on adjuvant chemotherapy and who had low preoperative serum albumin levels, than in those on a non-adjuvant chemotherapy regimen using the same parameters.

Generally, the normal range of serum albumin in an adult is defined as 3.5-5.0 g/dl. A level of ≤ 3.5 g/dl signifies hypoalbuminemia, while malnutrition and inflammation can inhibit albumin synthesis [8, 9]. It was shown in a systematic review of the epidemiological literature that an elevation in the serum albumin level decreases the risk of mortality in cancer patients [10]. Interestingly, the serum albumin level decreases the phosphorylation of the Rb proteins and increases p21 and p57 expression, which causes an increase in the G0/G1 cell population, as well as attenuating the cell proliferation of hepatocellular carcinoma [11]. A low serum albumin concentration is often found in the elderly and the possible effect of aging on albumin levels has been investigated by several scientists in order to describe the age-mediated decline in albumin [12, 13].

We proposed that stage III CRC patients in our study who received adjuvant chemotherapy (either XELOX or FOLFOX) would have higher five-year survival than those who did not, and that it would further have a positive impact on those with low preoperative serum albumin levels. The efficacy and safety of a single agent, such as bevacizumab and capecitabine, as maintenance therapy after first-line chemotherapy with XELOX or FOLFOX has been demonstrated in several studies [14-17].

In summary, we provided evidence that XELOX or FOLFOX attenuated tumor recurrence and metastasis and elevated five-year OS and RFS in patients with CRC. OS and RFS was greatest in those on FOLFOX adjuvant chemotherapy. It is likely that a favorable prognosis could be made in patients with stage III CRC with a serum albumin level of ≤ 3.5 g/dl following curatively resected CRC who are on a XELOX or FOLFOX adjuvant chemotherapy regimen.

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Disclosure of conflict of interest

None.

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