Efficacy of Postoperative Oxaliplatin- or Irinotecan-based Chemotherapy After Curative Resection of Synchronous Liver Metastases from Colorectal Cancer

HUNG-CHIH HSU[1,2], WEN-CHI CHOU[1,2], WEN-CHI SHEN[1,2], CHIAO-EN WU[1,2], JEN-SHI CHEN[1,2], CHI-TING LIAU[1,2], YUNG-CHANG LIN[1,2] and TSAI-SHENG YANG[1,2]

[1]*Division of Hematology-Oncology, Chang Gung Memorial Hospital at Linkou, Kwei-Shan, Tao-Yuan, Taiwan, R.O.C.;*
[2]*College of Medicine, Chang Gung University, Kwei-Shan, Tao-Yuan, Taiwan, R.O.C.*

Abstract. *Background: Postoperative 5-fluorouracil (5-FU)-based chemotherapy improves survival after resection of synchronous liver metastases from colorectal cancer (CRLM). We retrospectively assessed the efficacy of postoperative chemotherapy with a modern regimen containing of oxaliplatin or irinotecan after curative resection of synchronous CRLM. Patients and Methods: Seventy-two patients who received postoperative chemotherapy following curative resection of synchronous CRLM were analyzed. Patients were categorized into fluorouracil plus leucovorin (5-FU/LV, n=25), irinotecan-based regimen (FOLFIRI/IFL, n=21) and oxaliplatin-based regimen (FOLFOX, n=26) groups, according to the postoperative chemotherapy regimen. The clinicopathological parameters of patients were analyzed to evaluate clinical outcome. Results: Median relapse-free survival (RFS) was 14.4 months in the 5-FU/LV group vs. 20.8 months in the FOLFIRI/IFL group (p=0.032) and 18.8 months in the FOLFOX regimen (p=0.123). Median overall survival (OS) was >60 months in the FOLFOX and FOLFIRI/IFL groups vs. 38.5 months in the 5-FU/LV group (p=0.002 and p=0.019, respectively). In multivariate analysis, administrations of FOLFIRI/IFL or FOLFOX regimens were independent predictive factors for favorable RFS. Administration of the FOLFIRI/IFL regimen was the only independent predictive factor for favorable OS. Conclusion: Postoperative FOLFIRI/IFL and FOLFOX chemotherapy lead to more favorable RFS than 5-FU/LV following curative resection of synchronous CRLM.*

Correspondence to: Tsai-Sheng Yang, Division of Hematology-Oncology, Chang Gung Memorial Hospital at Linkou, 5 Fu-Hsing Street, Kwei-Shan, Tao-Yuan 333, Taiwan, R.O.C. Tel: +886 33281200 ext 8825, Fax: +886 32118800 ext 2362, a481124@adm.cgmh.org.tw

Key Words: Postoperative chemotherapy, colorectal liver metastasis, irinotecan, synchronous metastasis, oxaliplatin, 5-fluorouracil, leucovorin, FOLFOX, FOLFIRI.

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality, accounting for more than 600,000 deaths annually worldwide (1-3). In Taiwan, it is the second most common type of cancer in men and women, after hepatocellular carcinoma and breast cancer, respectively (4). The liver is the most common site of metastasis in CRC (50-60% of cases). One-third of patients have liver metastases at the time of diagnosis (synchronous) and two-thirds develop metastases during the disease course (metachronous) (5). Only 10-15% of CRCs with liver metastases (CRLM) are considered curable by resection (6). Those patients undergoing curative resection of primary and metastatic liver tumors have been reported to achieve near 35% 5-year survival rates (7). But most treatment failures are attributable to local hepatic recurrences or metastases to other sites in the first two years after surgery. Thus the question of whether postoperative chemotherapy should be used in this setting has been raised (8, 9).

In patients with stage III CRC, 5-fluorouracil (5-FU)-based chemotherapy following surgery provides significant improvements in disease-free survival (DFS) and overall survival (OS) compared to surgery-alone (10-12). This provides a rationale for its use as adjuvant treatment for patients with CRLM following complete resection of metastases. A pooled analysis based on two phase III trials showed that 138 patients who received 5-FU plus leucovorin (LV) chemotherapy after radical resection tended to have longer median progression-free survival (PFS) than the 140 patients who did not receive adjuvant chemotherapy (2.20 *vs.* 1.55 years, p=0.058). However, there was no statistically significant difference in OS (5.09 *vs.* 3.91 years, p=0.095) (6). Furthermore, a multicenter randomized trial of adjuvant 5-FU/LV for six months showed a significant benefit in terms of DFS with adjuvant chemotherapy compared to surgery alone (33.3 *vs.* 26.7%, p=0.028). In

addition, another study showed a trend towards higher 5-year survival rates with adjuvant chemotherapy (51.1 *vs*. 41.1%, p=0.13) (9). In patients with CRLM, randomized to receive postoperative local hepatic arterial infusion (HAI) with floxuridine in combination with intravenous continuous 5-FU or surgery alone, significant improvement was noted in the 4-year recurrence-free rate (46% *vs*. 25%) with the administration of adjuvant therapy (13). In addition, Wang X *et al*. showed that 5-FU-based chemotherapy following liver metastasectomy improved OS in the synchronous group but not the metachronous group (14). Thus, adjuvant chemotherapy with 5-FU and LV after resection of synchronous CRLM has been demonstrated to significantly improve DFS and show a trend towards significant benefit in terms of OS.

More advanced oxaliplatin- and irinotecan-based chemotherapy regimens have established their roles in improving the survival of patients with metastatic CRC. They may also have a role in improving DFS or even OS in the postoperative setting following curative resection of synchronous CRLM. A randomized study comparing two postoperative chemotherapy regimens, FOLFIRI (irinotecan and infusional 5-fluorouracil with leucovorin) and 5-FU/LV, demonstrated no difference in either PFS or OS between the two treatment arms. However, in the patients treated within 42 days of surgery, the FOLFIRI group appeared to do better than the 5-FU/LV group in terms of PFS (p=0.17) (15). This study was unable to confirm the better postoperative regimen for synchronous CRLM because of the heterogeneous population of patients (synchronous and metachronous) and the effect of previous adjuvant chemotherapy. There is little consensus regarding the effect of postoperative chemotherapy regimens after resection of synchronous CRLM. In the present study, we retrospectively investigated the efficacy of oxaliplatin-based, irinotecan-based and 5-FU-based postoperative chemotherapy after curative resection of synchronous CRLM.

Patients and Methods

Patients. We retrospectively reviewed the medical records of patients with synchronous CRLM at the Chang Gung Memorial hospital at Linko, Taiwan between January 1994 and December 2010. A total of 72 patients were included in the present study. All patients met the following criteria: (i) histologically proven colorectal adenocarcinoma; (ii) any number and any site of liver metastases which could be curatively resected; (iii) synchronous limited liver metastases with no extrahepatic metastases both in preoperative clinical imaging studies and postoperative pathological findings; (iv) curative resection (R0 resection) of both primary colorectal cancer and liver metastases; and (v) patients received postoperative chemotherapy. The patients with following characteristics were excluded (i) histology other than adenocarcinoma; (ii) grossly or microscopic residual disease postoperatively at the primary sites or in the liver (R1 or R2 resection). All patients had good performance status (ECOG: 0-1) and did not receive preoperative therapy such as chemotherapy or radiotherapy.

They would receive postoperative chemotherapy for 6-8 months. The study was conducted with the approval of the Ethics Committee of the University of Chang Gung Memorial hospital at Linkou (102-0045B).

Clinical characteristics. The demographic and clinical characteristics were determined from the medical records. They include gender, age, tumor histological grade, primary tumor location, preoperative carcinoembryonic antigen (CEA) level, and time from surgery to chemotherapy, as well as sites of metastases, number of liver metastases, maximal size of liver metastases and extent of liver surgery.

Liver metastatic tumor resection. Before surgery, all patients were thoroughly evaluated with appropriate imaging studies, including computed tomography (CT) of the abdominal and pelvic areas, chest roentgenography, and/or chest CT, to determine the clinical status of the CRC and hepatic metastases. Resectability with curative intent required complete resection of all hepatic metastatic lesions and acceptable residual liver function after resection. Liver-metastatic tumor resection was performed using either the surgical clamp-crush technique or the Cavitron Ultrasonic Surgical Aspirator (CUSA; Valleylab, Inc., Boulder, CO, USA). The extent of liver surgery was defined according to Couinaud's classification of liver segments.

Postoperative chemotherapy. Patients were divided into the following three groups according to their postoperative chemotherapy regimen: (i) 5-FU /LV regimen, (ii) irinotecan-based regimen (FOLFIRI (irinotecan and infusional 5-fluorouracil with leucovorin)/IFL (irinotecan and bolus 5-fluorouracil with leucovorin), and (iii) oxaliplatin-based regimen (FOLFOX) (oxaliplatin and infusional 5-fluorouracil with leucovorin). The 5-FU/LV regimen included intravenous (iv) 5-FU/LV regimen, such as the Mayo regimen (5-FU 370-425 mg/m^2/d iv bolus d1-5, leucovorin 20-25 mg/m^2/d iv bolus d1-5, q4w × 6 cycles) (16), RPMI regimen (5-FU 500 mg/m^2 iv bolus 1 h after the start of leucovorin, leucovorin 500 mg/m^2 iv over 2 h qw × 6 weeks every 8 weeks for 3-4 cycles) (17), or AIO regimen (5-FU 2.6-3 g/m^2/day iv over 24 h with or without LV 20-500 mg/m^2/day iv weekly for 6 weeks, with 2-week rests between cycles for 3-4 cycles) (18). Oral 5-FU and its derivatives such as tegafur/uracil (UFT) (UFT 100 mg/m^2 po every 8 hours × 4 weeks and leucovorin (LV) 30 mg po every 8 hours × 4 weeks) and capecitabine (capecitabine 1250 mg/m^2 po bid × 14 days q3w × 8 cycles), were also included. Irinotecan-based regimens included IFL (Leucovorin 20 mg/m^2 iv bolus qw × 4 weeks every 6 weeks, 5-FU 500 mg/m^2 iv bolus qw × 4 weeks every 6 weeks, irinotecan 125 mg/m^2 iv qw × 4 weeks every 6 weeks for 4 cycles) (19) and FOLFIRI regimen (Leucovorin 400 mg/m^2 iv over 2 h before 5-FU d1, 5-FU 400 mg/m^2 iv bolus d1, and then 2400 mg/m^2 iv over 46 h, irinotecan 180 mg/m^2 iv over 90 min d1 every 2 weeks for 12 cycles) (20). The oxaliplatin- based regimen included FOLFOX6 (Leucovorin 400 mg/m^2 iv over 2 hours before 5-FU d1, 5-FU 400 mg/m^2 iv bolus d1 followed by 2400 mg/m^2 iv over 46 hours, oxaliplatin 100 mg/m^2 iv over 2 h d1, every 2 weeks for 12 cycles) and mFOLFOX6 (Leucovorin 400 mg/m^2 iv over 2 hours before 5-FU d1, 5-FU 400 mg/m^2 iv bolus d1 followed by 2400 mg/m^2 iv over 46 hours, oxaliplatin 85 mg/m^2 iv over 2 hours d1 every 2 weeks × 12 cycles) (21-22). Toxicity was evaluated using Common Terminology Criteria for Adverse Events, version 3.0 (23).

Table I. *Demographics and characteristics of patients with regard to postoperative chemotherapy after curative resection of synchronous colorectal cancer with limited liver metastases.*

Characteristic	Postoperative chemotherapy			Total no.	*p*-Value*
	5-FU/LV, no.	FOLFIRI/IFL, no.	FOLFOX, no.	(%)	
Total	25	21	26	72	
Age (median: 58, range: 26-76), years					
>60	13	13	9	35 (51%)	0.162
<60	12	8	17	37 (49%)	
Gender					
Female	11	10	8	29 (40%)	0.451
Male	14	11	18	43 (60%)	
Primary tumor					
Rectum	15	10	10	35 (51%)	0.304
Colon	10	11	16	37 (49%)	
Histological grade					
Well-differentiated	1	0	2	3 (4%)	0.734
Moderately-differentiated	22	20	22	64 (89%)	
Poorly-differentiated	2	1	2	5 (7%)	
Number of liver metastases					
<2	16	11	10	37 (51%)	0.188
≥2	9	10	16	35 (49%)	
Maximum size of liver metastases					
<3cm	15	10	16	41 (57%)	0.587
≥3cm	10	11	10	31 (43%)	
Distribution of liver metastases					
Unilobar	20	17	19	56 (78%)	0.769
Bilobar	5	4	7	16 (22%)	
Extent of liver surgery					
<3 segments	16	14	17	47 (65%)	0.982
≥3 segments	9	7	9	25 (35%)	
Time from surgery to chemotherapy					
≤6 weeks	17	16	24	57 (79%)	0.094
>6 weeks	8	5	2	15 (21%)	
Pre-surgery CEA (ng/ml)					
≤50	9	4	9	22 (31%)	0.394
>50	16	17	17	50 (69%)	

*Chi-square; Performance status all are 0; CEA: carcinoembryonic antigen; 5-FU/LV: 5-fluorouracil/leucovorin; FOLFIRI: irinotecan and infusional 5-fluorouracil with leucovorin; IFL: irinotecan and bolus 5-fluorouracil with leucovorin; FOLFOX: oxaliplatin and infusional 5-fluorouracil with leucovorin.

Statistical analysis. Relapse-free survival (RFS) was calculated from the date of resection of synchronous CRLM to the date of proven relapse, or death. For patients lost to follow-up, data were censored on the date when the patient was last seen alive without recurrence. OS was calculated from the date of resection of CRLM until the date of death from any cause. For patients lost to follow-up, data were censored on the date when the patient was last seen alive. RFS, OS, and 5-year survival rate were estimated by using the Kaplan–Meier method. Comparisons between groups were performed using the *t*-test, Chi-square or Fisher's exact test. The differences between factors were evaluated by using the log-rank test. The factors included chemotherapy regimen, age, gender, histological grade and origin of primary tumor, maximum size of liver metastases, number of liver metastases, extent of liver surgery, distribution of liver metastases, time from surgery to start of chemotherapy and preoperative serum CEA. All factors were recruited into the Cox regression model. Hazard ratios (HRs) are presented with their 95% confidence intervals (CIs). All statistical tests were two-sided, and $p<0.05$ was considered statistically significant. All statistical analyses were performed using PASW version 18.0 for Windows (SPSS Inc., Chicago, IL., USA).

Results

Patients' characteristics. The demographic and clinical characteristics of the patients are summarized in Table I. The study population comprised of 43 male and 29 female patients with a median age of 58 years. All patients had an ECOG performance status of 0. The location of the primary tumor was the colon in 37 patients (51%) and the rectum in 35 patients (49%). All patients with synchronous CRLM had undergone R0 resection. The number of liver metastases was fewer than two in 37 patients (51%) and two or more in 35

Table II. *Adverse events of chemotherapy.*

Adverse event	Chemotherapy regimen					
	5-FU/LV		FOLFIRI/IFL		FOLFOX	
	All grades no. (%)	Grade 3/4 no. (%)	All grades no. (%)	Grade 3/4 no. (%)	All grades no. (%)	Grade 3/4 no. (%)
Hematological toxicity						
Anemia	6 (24%)	0	13 (62 %)	0	13 (50%)	0
Thrombocytopenia	1 (4%)	1 (4%)	1 (4.7%)	1 (4.7%)	7 (27%)	2 (7.6%)
Neutropenia	3 (12%)	0	10 (48%)	4 (19%)	17 (65%)	5 (19.2%)
Neutropenia fever	0	0	0	0	1 (3.8%)	1 (3.8%)
Non-hematologic toxicity						
Nausea	5 (20%)	0	12 (57%)	1 (4.7%)	9 (34.6%)	0
Vomiting	4 (16%)	0	12 (57%)	1 (4.7%)	11 (42%)	0
Allergy	0	0	0	0	1 (3.8%)	1 (3.8%)
Stomatitis	9 (36%)	2 (8%)	1 (4.7%)	0	0	0
Neuropathy	1 (4%)	0	0	0	18 (69%)	1 (3.8%)
Diarrhea	3 (12%)	0	13 (62%)	6 (28.5%)	5 (19.2%)	0
Hand foot syndrome	1 (4%)	0	0	0	0	0

5-FU/LV: 5-Fluorouracil/leucovorin; FOLFIRI: irinotecan and infusional 5-fluorouracil with leucovorin; IFL: irinotecan and bolus 5-fluorouracil with leucovorin; FOLFOX: oxaliplatin and infusional 5-fluorouracil with leucovorin.

patients (49%). When considering time from surgery to start of chemotherapy, 57 patients (79%) received chemotherapy within 6 weeks after surgery and 15 patients (21%) received chemotherapy more than 6 weeks after surgery (Table I).

Postoperative chemotherapy and toxicity. Among the 72 patients that received postoperative chemotherapy, only seven patients did not complete chemotherapy due to tumor recurrence (5-FU/LV group: two patients, FOLFOX group: three patients, FOLFIRI/IFL group: two patients). Table II shows the treatment-related adverse effects reported for each group. Generally, these toxicities were mild and manageable. No treatment-related mortality was noted in the present study.

Survival. The median follow-up time was 38.8 months. The median RFS in the FOLFIRI/IFL group was significantly better than that in the 5-FU/LV group (20.8 *vs*. 14.5 months, $p=0.032$) (Figure 1). In contrast, the median RFS of the FOLFOX group was not significantly better than that of the 5-FU/LV group (18.9 *vs*. 14.5 months, $p=0.123$) (Figure 1). However, the 3- year and 4-year RFS rates in the FOLFOX group were significantly better than those in the 5-FU/LV group (both 3- and 4-year RFS rates: 30.8% *vs*. 8%, $p=0.041$) (Figure 1). The median OS in the5-FU/LV group was 49 months and this was not reached (>60 months) in either the FOLFOX or the FOLFIRI/IFL group (FOLFOX *vs*. 5-FU/LV $p=0.019$, FOLFIRI/IFL *vs*. 5-FU/LV $p=0.002$) (Figure 2). The 3- and 5-year OS rates were 77% and 63% in the FOLFOX group, 94% and 53% in the FOLFIRI/IFL group, and 48% and 13% in the 5-FU/LV group (Figure 2). In multivariate analysis, FOLFIRI/IFL chemotherapy was the only significant independent factor for predicting favorable RFS and OS (HR=0.421, $p=0.015$ and HR=0.190, $p=0.001$ respectively) (Tables III and IV). However, FOLFOX chemotherapy had favorable RFS but not OS in multivariate analysis (HR=0.477, $p=0.046$ and HR=0.365, $p=0.078$ respectively) (Table III and IV).

Relapse pattern and second-line therapy. A total of 58 out of 72 patients (80%) had relapse with a median time to relapse of 14.5 months. The predominant sites of relapse were the liver (94%), lung (15%) and both the liver and lung (5%) (Table V). Eighteen out of the 58 patients (31%) underwent curative metastectomy (15 patients: liver metastectomy, four patients: lung metastectomy). One patient developed local recurrence and underwent curative resection again. Forty-seven patients (81%) received second-line systemic chemotherapy. One patient received radiotherapy for brain metastases and 7 patients did not receive any therapy because of poor performance status after relapse (Table V).

Discussion

Curative surgery has become a well-established therapy for CRLM in both the synchronous and metachronous setting because of the improvement in OS. Postoperative chemotherapy using 5-FU/LV regimens has shown a significant clinical benefit, supported by data from larger

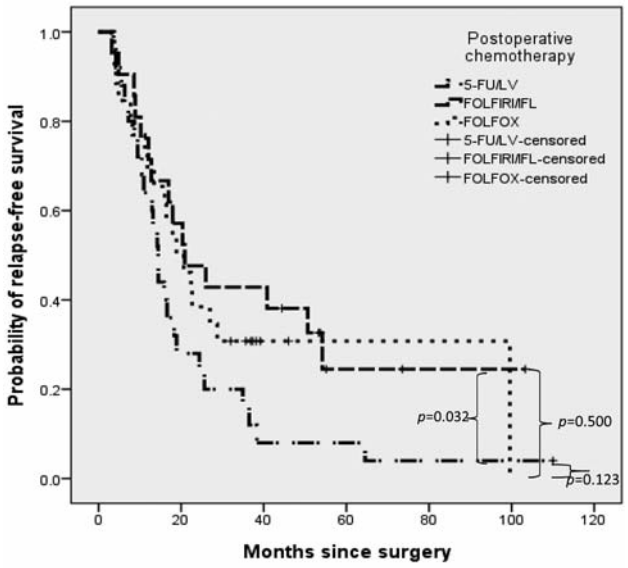

Figure 1. *Relapse-free survival by postoperative chemotherapy with FOLFOX (oxaliplatin and infusional 5-fluorouracil with leucovorin), FOLFIRI/IFL (irinotecan and infusional 5-fluorouracil with leucovorin / irinotecan and bolus 5-fluorouracil with leucovorin) and 5-FU/LV (5-fluorouracil / leucovorin) following resection of synchronous colorectal liver metastases. p-Value by log-rank test.*

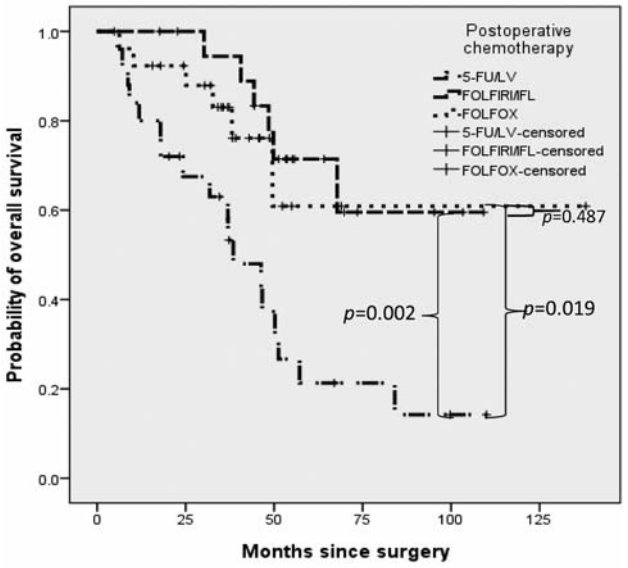

Figure 2. *Overall survival by postoperative chemotherapy with FOLFOX (oxaliplatin and infusional 5-fluorouracil with leucovorin), FOLFIRI/IFL (irinotecan and infusional 5-fluorouracil with leucovorin / irinotecan and bolus 5-fluorouracil with leucovorin) and 5-FU/LV (5-fluorouracil / leucovorin) following resection of synchronous colorectal liver metastases. p-Value by log-rank test.*

studies (24-25) and combined analysis of two phase III trials (6). The clinical benefit was more significant in the group with synchronous CRLM than in the metachronous group. Recent progress in the development of anti-cancer drugs including oxaliplatin and irinotecan has markedly improved the prognosis of patients with unresectable metastatic CRC (26). However, the role of these drugs in the postoperative setting after resection of synchronous CRLM is still unknown. Therefore we decided to evaluate the benefit of postoperative oxaliplatin- and irinotecan-based chemotherapy for synchronous CRLM.

The present study showed that irinotecan-based chemotherapy (FOLFIRI/IFL) had a more significant benefit in terms of RFS and OS than did 5-FU/LV chemotherapy in the postoperative setting after resection of synchronous CRLM. In contrast, Ychou *et al*. (15) found no difference in RFS and OS between patients in the FOLFIRI arm and 5-FU/LV arm following complete resection of CRLM, perhaps due to the effect of their heterogeneous population (synchronous and metachronous) and to prior adjuvant chemotherapy. These two factors most likely diminished the efficacy of FOLFIRI for synchronous CRLM.

Oxaliplatin-based chemotherapy (FOLFOX6 and mFOLFOX6) led to better RFS than the 5-FU/LV regimen, as shown by multivariate analysis in our study. However, the FOLFOX regimen only showed a trend towards predicting favorable OS in multivariate analysis. This phenomenon was likely caused by the small sample size and relatively short follow-up duration of censored patients. Hence, the marginally significant difference in RFS did not translate into OS. In terms of OS estimated by Kaplan–Meier method, oxaliplatin-based chemotherapy led to better OS than 5-FU/LV chemotherapy. Kim *et al*. and Nozawa *et al*. (27, 28) also showed that FOLFOX chemotherapy improved OS and RFS compared with 5-FU/LV chemotherapy after resection of synchronous CRLM. Unlike the present study which included more patients and direct comparisons between three treatment arms, another study included only six patients with FOLFOX and yet another study used a historical control for the 5-FU/LV regimen (27, 28). A randomized phase II/III study in Japan, JCOG0603, which started in spring 2007 and is currently ongoing, aims to address the superiority of postoperative mFOLFOX6 over surgery alone in patients with resectable CRLM (29).

The efficacy of oxaliplatin-based chemotherapy and irinotecan-based chemotherapy in improving OS and RFS benefit was similar in the present study (FOLFOX and FOLFIRI/IFL, median OS> 60 months, p=0.487, FOLFOX RFS, 18.9 months, and FOLFIRI/IFL RFS, 20.9 months, p=0.500). This result was similar to the efficacy of oxaliplatin-based chemotherapy and irinotecan-based chemotherapy recorded for unresectable metastatic CRC, but it was different from that of adjuvant oxaliplatin-based chemotherapy and irinotecan-based chemotherapy in patients

Table III. *Univariate analysis associated with relapse-free survival and overall survival.*

		Relapse-free survival		Overall survival	
Factor	Patients no	Median survival (months)	*p*-value*	Median survival(months)	*p*-value*
Postoperative chemotherapy					
5-FU/LV	25	14.5	-	38.5	-
FOLFIRI/IFL	21	20.8	0.032	Not reached	0.002
FOLFOX	26	18.9	0.123	Not reached	0.019
Age, years					
≥60	35	17.9	0.704	57.2	0.800
<60	37	17.9		51.2	
Gender					
Female	29	14.5	0.871	49.8	0.326
Male	43	18.3		67.8	
Primary tumor					
Rectum	37	18.9	0.430	67.8	0.598
Colon	35	15.9		57.2	
Histological grade					
Well-differentiated	3	18.9	-	45	-
Moderately-differentiated	64	17.9	0.726	57.1	0.358
Poorly-differentiated	5	7,2	0.373	10.5	0.127
Number of liver metastases					
<2	37	16.6	0.968	50.2	0.314
≥2	35	20.6		84.1	
Maximum size of liver metastases					
<3 cm	41	17.9	0.330	51.2	0.911
≥3 cm	31	17.9		67.8	
Distribution of liver metastases					
Unilobar	56	16.6	0.718	57.2	0.817
Bilobar	16	20,4		67.8	
Extent of liver surgery					
<3 segments	47	16.9	0.344	51.2	0.777
≥3 segements	25	20.3		57.2	
Time from surgery to chemotherapy					
≤6 weeks	57	17.9	0.533	51.2	0.829
>6 weeks	15	17.9		Not reached	
Pre-surgery CEA (ng/ml)					
≤50	22	18.8	0.769	51.2	0.889
>50	50	16.6		57.2	

*log rank test; CEA: carcinoembryonic antigen; 5-FU/LV: 5-fluorouracil/leucovorin; FOLFIRI: irinotecan and infusional 5-fluorouracil with leucovorin; IFL: irinotecan and bolus 5-fluorouracil with leucovorin; FOLFOX: oxaliplatin and infusional 5-fluorouracil with leucovorin.

with stage III CRC. Therefore, patients with synchronous CRLM might be treated similarly to patients with unresectable metastatic CRC even in the postoperative setting.

Compared with OS and RFS following resection of metachronous CRLM (30), the present study showed poor prognosis for synchronous CRLM. Wang *et al*. also yielded the same result (14). Our study as well as that by Nozawa *et al*. (28) demonstrated that FOLFOX regimen can improve RFS benefit in patients with synchronous CRLM after resection. However, no benefit in terms of RFS was seen for the metachronous group in the study by Nozawa *et al*. (28). A plausible explanation for this discrepancy is that previous chemotherapy had conferred chemoresistance on the tumor cells and thus diminished the survival benefit afforded by chemotherapy in the metachronous group. This explanation is supported by the fact that a significantly quantitative difference in expression of thymidylate synthase (TYMS) and excision repair cross-complementing factor-1 (ERCC1) expression was noted between the liver metastases and their respective primaries in the metachronous group, but not in synchronous group (31). TYMS and ERCC1 expression were related to 5-FU resistance and platinum (oxaliplatin) resistance respectively (32, 33). This phenomenon was also observed in the CARIO study, which showed a lower response rate in patients with metachronous metastases than in those with synchronous metastases from CRC (34).

Table IV. *Multivariate analysis associated with relapse-free survival and overall survival.*

	Relapse-free survival			Overall survival		
Factor	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Postoperative chemotherapy						
5-FU/LV	1		-	1	-	
FOLFIRI/IFL	0.421	0.209-0.847	0.015	0.190	0.068-0.527	0.001
FOLFOX	0.477	0.230-0.988	0.046	0.365	0.119-1.119	0.078
Age, years						
<60	1			1		
≥60	0.852	0.461-1.576	0.610	1.341	0.560-3.213	0.511
Gender						
Female	1			1		
Male	1.195	0.633-2.256	0.582	0.598	0.250-1.428	0.247
Primary tumor						
Rectum	1			1		
Colon	1.049	0.596-1.849	0.868	1.005	0.443-2.282	0.990
Histological grade						
Well-differentiated	1		-	1	-	
Moderately-differentiated	1.160	0.223-6.032	0.860	16182.736	0-1.111E152[a]	0.955
Poorly-differentiated	2.812	0.442-17.898	0.274	78326.002	0-5.382E152[b]	0.948
Number of liver metastases						
<2	1			1		
≥2	1.194	0.590-2.417	0.621	0.551	0.176-1.726	0.306
Maximum size of liver metastases						
<3 cm	1		1	1		
≥3 cm	0.674	0.343-1.324	0.252	1.215	0.446-3.304	0.703
Distribution of liver metastases						
Unilobar	1			1		
Bilobar	1.291	0.571-2.919	0.540	2.662	0.698-10.150	0.152
Extent of liver surgery						
<3 segments	1		0.343	1		
≥3 segments	0.695	0.343-1.324		0.915	0.336-2.496	0.863
Time from surgery to chemotherapy						
≤6 weeks	1			1		
>6 weeks	1.149	0.562-2.347	0.562	1.136	0.399-3.234	0.811
Pre-surgery CEA (ng/ml)						
≤50	1			1		
>50	1.760	0.878-3.530	0.111	0.915	0.446-3.304	0.863

a: 1.111×10152; b: 5.382×10152; CEA: carcinoembryonic antigen; 5-FU/LV: 5-fluorouracil/leucovorin; FOLFIRI: irinotecan and infusional 5-fluorouracil with leucovorin; IFL: irinotecan and bolus 5-fluorouracil with leucovorin; FOLFOX: oxaliplatin and infusional 5-fluorouracil with leucovorin.

In the present study, eight out of 24 patients (33%) with relapse in the 5-FU/LV group still received similar chemotherapy again because there was no choice of new regimens during the 1990s. This might be one reason why the 5-FU/LV group had unfavorable OS compared with the FOLFOX and FOLFIRI/IFL group.

To conclude, when compared to 5-FU/LV postoperative chemotherapy treatment, an irinotecan-based regimen was beneficial for improving OS and RFS in patients with synchronous CRLM. Oxaliplatin-based chemotherapy led to better RFS than 5-FU/LV but showed only a trend toward favorable OS in multivariate analysis. To our knowledge, this is the first report on the better efficacy of FOLFOX and FOLFIRI/IFL in terms of RFS and OS compared with 5-FU/LV following curative resection of synchronous CRLM. The present study indicates that patients with synchronous CRLM might be treated with chemotherapy regimens used in the postoperative setting for patients with metastatic CRC, rather those used in the adjuvant setting for patients with stage IIII CRC. Therefore it is important to design a prospective large-scale randomized clinical trial using FOLFOX, FOLFIRI and other promising regimens such as cetuximab or bevacizumab, for patients with curatively resected synchronous CRC plus liver or other organ metastases. This will hopefully facilitate the establishment of a treatment for improved clinical benefit in the future.

Table V. *Relapse pattern and subsequent treatment in 58 patients after curative resection of synchronous colorectal cancer with limited liver metastases.*

Characteristic (%)	Postoperative chemotherapy			Total no.
	5-FU/LV no.	FOLFIRI/IFL no.	FOLFOX no.	
No. of Relapse/total patients	24/25 (96%)	15/21 (71%)	19/26 (73%)	58/72 (81%)
Relapse pattern (n=58)				
Hepatic relapse	22	10	13	55 (94%)
Lung relapse	1	4	4	9 (15%)
Local relapse	1	0	0	1 (2%)
Other (peritoneum, ovary, pleura, brain, distal lymph node)	4	2	4	10 (17%)
Therapy after relapse (n=58)				
Surgery	4	6	8	18 (31%)
Liver metastectomy	4	4	7	15
Lung metastectomy	1	2	1	4
Local surgery	1	0	0	1
Radiotherapy (brain)	0	1	0	1 (2%)
Chemotherapy	18	10	19	47 (81%)
5-FU-based	8	3	1	12
Oxaliplatin-based	4	7	1	12
Irinotecan-based	6	0	17	23
No treatment	5	2	0	7 (12%)

5-FU/LV: 5-Fluorouracil/leucovorin; FOLFIRI: irinotecan and infusional 5-fluorouracil with leucovorin; IFL: irinotecan and bolus 5-fluorouracil with leucovorin; FOLFOX: oxaliplatin and infusional 5-fluorouracil with leucovorin.

Conflicts of Interest

There are no potential conflicts of interest.

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Received May 16 2013
Revised June 14, 2013
Accepted June 17, 2013