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Prognostic Factors for Recurrence after Tegafur-uracil Plus Leucovorin Adjuvant Chemotherapy in Patients with Colorectal Cancer

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Abstract: To evaluate prognostic factors for recurrence after tegafur-uracil plus leucovorin (UFT / LV) adjuvant chemotherapy in patients with colorectal cancer (CRC). Consecutive patients with CRC who received UFT / LV as adjuvant chemotherapy at Showa University Hospital between June 2005 and December 2008 were included in the study, 5-year disease-free survival (DFS) and overall survival (OS) rates were estimated, and prognostic factors for recurrence were analyzed using the Cox proportional hazards model for multivariate analysis. Of 92 patients included in the study, 17 (18.5%) had disease recurrence. The 5-year DFS and OS rates were 82.2% and 91.9%, respectively. In the multivariate analysis, preoperative CA19-9 level ＞ 37 U / ml, emergency operation, and T4 lesions were independent significant prognostic factors after treatment with UFT / LV adjuvant chemotherapy. The three independent prognostic factors —T4 lesions, emergency operation, and high preoperative CA19-9 levels— may be useful for decision-making regarding whether patients should receive 5-fluouracil-based or L-oxaliplatin-based adjuvant chemotherapy. As this was a single-institution study with a small number of patients, our findings need to be confirmed in larger multicenter studies..

Key words: adjuvant chemotherapy, colorectal cancer, UFT / LV, long-term outcomes, prognostic factors

Introduction

In patients with cancer, postoperative adjuvant chemotherapy reduces disease recurrence and improves overall survival. Such benefits for patients with Stage Ⅲ colorectal cancer (CRC) are great enough to recommend adjuvant chemotherapy[1]. Based on the results from the Japan Clinical Oncology Group (JCOG0205)[2] and the National Surgical Adjuvant Breast and Bowel Protocol (NSABP C-06)[3], a regimen of uracil and tegafur plus leucovorin (UFT / LV) has been widely used as standard postoperative adjuvant chemotherapy for Stage Ⅲ CRC in Japan.

L-oxaliplatin (L-OHP)-based adjuvant chemotherapy such as FOLFOX (oxaliplatin plus infusional leucovorin and fluorouracil)[4] and 5-fluouracil (5-FU)-based adjuvant chemotherapy such as capcitabine[5] or 5-FU / LV are also used as standard adjuvant chemotherapy for Stage Ⅲ

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CRC in Japan[6]. Furthermore, based on the results of the Adjuvant Chemotherapy Trial of TS-1 for Colon Cancer (ACTS-CC) trial[7], which demonstrated non-inferiority of S-1 compared with UFT / LV for Stage Ⅲ colon cancer, S-1 will also be a new adjuvant chemotherapy option for colon cancer. However, clinically useful predictors that can help select adjuvant chemotherapy regimens have not been identified. Although various findings in patients with Stage Ⅱ CRC, including poorly differentiated histology, T4 lesions, perforation, and inadequately sampled lymph nodes ($n < 13$), have been considered for use in selection of adjuvant chemotherapy[8–10], there is no international consensus. Therefore, we evaluated long-term outcomes and prognostic factors for recurrence after UFT / LV adjuvant chemotherapy in patients with Stage Ⅱ or Ⅲ CRC and identified potential selection criteria for UFT / LV as adjuvant chemotherapy.

Materials and methods

Patients

From June 2005 to December 2008, consecutive patients who received oral UFT / LV as adjuvant chemotherapy only for CRC at Showa University Hospital were prospectively enrolled. The main inclusion criteria for treatment with UFT / LV adjuvant chemotherapy were : histologically proven Stage Ⅱ or Ⅲ colorectal adenocarcinoma, an Eastern Cooperative Oncology Group performance status (PS) of ≤ 1, no prior chemotherapy or radiotherapy for CRC, and adequate bone marrow, renal and hepatic function.

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients, with the approval of the ethics committee of Showa University Hospital.

Treatment protocol

We administered chemotherapy to all eligible patients between 3 and 6 weeks after surgery. UFT (300 mg / m^2 / day) and LV (75 mg / body / day) were administered orally on days 1–28, followed by a 7-day rest period ; this 35-day cycle was repeated up to five times. The daily UFT and LV doses were divided into three doses that were given 8 h apart with water. Patients were instructed to avoid consuming food during the hour before and the hour after each dose. Additional details and toxicity assessments have been described elsewhere[11].

Patient follow-up and recurrence of disease

After completing chemotherapy, patients were scheduled for follow-up as outpatients every 3 months during the first 3 years, every 6 months during the next 2 years, and annually thereafter, as per the 2010 Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines[6]. Levels of serum tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9]) were measured every 3 months for the first 3 years and every 6 months for the next 2 years. Computed tomography (CT) scans of the chest, abdomen, and pelvis were performed every 6 months for 5 years. Colonoscopies were performed every 12 months for 3 years.

Local recurrence was defined as clinical or radiologic tumor regrowth within the previous pelvic treatment field, peritoneum, or anastomosis. Distant recurrence was defined as tumor growth in any other area. Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up. Disease-free survival (DFS) was defined as the period from the date of surgery to the date of recurrence or last follow-up.

Clinical and pathological variables

The patient characteristics that we recorded included age, sex, PS, tumor location, preoperative CEA and CA19-9 levels, histologic type, tumor size, depth of tumor, lymphatic and venous invasion, number of lymph node (LN) metastases, degree of LN metastases, pathological stage, surgical approach and procedure, level of LN dissection, number of LNs examined, and postoperative complications. DFS, OS, and the relationship between clinicopathological variables and development of recurrence were analyzed. The level of LN dissection and histologic types were evaluated according to the Japanese Classification of Colorectal Carcinoma, Second English Edition[12]. Depth of tumor, degree of LN metastases, and pathological stage were categorized according to the Seventh Edition of the TNM Classification (TNM7th)[13].

Statistical analysis

Continuous variables are expressed as medians and ranges. Categorical variables are expressed as numbers and percentages. The relationship between clinicopathological variables and development of recurrence were assessed by univariate analyses using Cox proportional hazards regression models and are expressed as hazard ratios and 95% confidence intervals (CIs). All factors with a p value of <0.05 were introduced into multivariate Cox regression analyses with a semi-manual backward (likelihood ratio) variable selection. The 5-year DFS and OS rates were estimated using the Kaplan–Meier method. Finally, based on the number of prognostic factors for recurrence, DFS and OS were compared using a log-rank test and Wilcoxon test. All statistical analyses were performed using JMP® Pro version 11.0.0 software (SAS Institute, Cary, NC, USA) and p values of <0.05 were considered statistically significant.

Results

Patient characteristics and surgical outcomes

A total of 92 patients were enrolled in the study. Patient characteristics and surgical outcomes are summarized in Table 1. Emergency operations were performed for two patients (2.2%) due to tumor perforation.

Evolution of disease

The median follow-up period was 70 months (range, 9–120 months). Seventeen patients (18.5%) developed disease recurrence; their characteristics are listed in Table 2. Eight of them (47.1%) had local recurrence (median time to relapse, 23.3 months) — three developed peritoneal recurrences, and five developed anastomotic recurrences. The other nine (52.9%)

Table 1. Patient characteristics and surgical outcomes (N = 92)

Age (years)	Median (range)	67 (30-84)
Sex	M / F	60 / 32
PS (ECOG), N (%)	0	70 (76.1)
	1	22 (23.9)
Tumor location, N (%)	Right-side colon (C, A, T)	29 (31.5)
	Left-side colon (D, S)	27 (29.3)
	Rectum	36 (39.1)
Preoperative CEA level (ng / ml), N (%)	≦ 5.1	45 (48.9)
	> 5.1	32 (34.8)
	Unknown	15 (16.3)
Preoperative CA19-9 level (U / ml), N (%)	≦ 37	66 (71.7)
	> 37	9 (9.8)
	Unknown	17 (18.5)
Histologic types[a], N (%)	Papillaly	1 (1.1)
	Tublar	82 (89.1)
	poorly	6 (6.5)
	Mucinous	3 (3.3)
Tumor size (mm)	Median (range)	45 (17-90)
Depth of tumor (TNM 7th), N (%)	T1	1 (1.1)
	T2	5 (5.4)
	T3	63 (68.5)
	T4a	14 (15.2)
	T4b	9 (9.8)
Lymphatic invasion, N (%)	Negative	21 (22.8)
	Positive	71 (77.2)
Venous invasion, N (%)	Negative	15 (16.3)
	Positiv	77 (83.7)
No. of LN metastases, (N)	Median (range)	0 (0-7)
LN metastasis (TNM 7th), N (%)	N0	52 (56.5)
	N1a	23 (25.0)
	N1b	13 (14.1)
	N2a	3 (3.3)
	N2b	1 (1.1)
Stage (TNM7th), N (%)	Ⅱ A	43 (46.7)
	Ⅱ B	4 (4.4)
	Ⅱ C	5 (5.4)
	Ⅲ A	12 (13.0)
	Ⅲ B	22 (23.9)
	Ⅲ C	6 (6.5)
Operation, N (%)	Elective	90 (97.8)
	Emergency	2 (2.2)
Surgical approach, N (%)	Laparoscopic	40 (43.5)
	Laparotomy	52 (56.5)
Surgical procedure, N (%)	Colectomy	57 (62.0)
	HAR	11 (11.9)
	LAR	11 (11.9)
	uLAR	7 (7.6)
	Hartmann	1 (1.1)
	APR	5 (5.4)
Level of LN dissectiona, N (%)	D1	2 (2.2)
	D2	36 (39.1)
	D3	54 (58.7)
No. of LNs examined, (N)	Median (range)	20 (4-52)
Operating time (min)	Median (range)	200 (95-735)
Operative blood loss (ml)	Median (range)	120 (3-1070)
Complications, N (%)	None	70 (76.1)
	Superficial SSI	7 (7.6)
	Organ / space SSI	2 (2.2)
	Paralytic ileus	11 (11.9)
	Remote infections	2 (2.2)
Length of hospital stay (day)	Median (range)	11 (4-51)

Remote infections were pneumonia and a urinary tract infection
PS Peformance status, *ECOG* Eastern Cooperative Oncology Group,
C Cecum, *A* Ascending colon, *T* Transverse colon, *D* Descending colon, *S* Sigmoid colon
CEA Carcinoembryonic antigen, *CA19-9* Carbohydrate antigen 19-9
HAR High anterior resection, *LAR* Low anterior resection,
uLAR Ultra-low anterior resection, *APR* Abdominoperineal resection,
LN Lymph node, *SSI* Surgical site infection
[a] Japanese Classification of Colorectal Carcinoma, Second English Edition (12)

developed distant recurrences (median time to relapse, 15.1 months) — three, three, two and one developed metastases of the liver, lungs, distant lymph nodes, and omentum, respectively. When recurrences were categorized according to stage (TNM7th), four patients (23.5%) were in stage ⅡA, two (11.8%) were in ⅡB, three (17.6%) were in ⅡC, two (11.8%) were in ⅢA, four (23.5%) were in ⅢB, and two (11.8%) were in ⅢC.

As the first treatment for recurrence, eight patients underwent an operation, five patients received L-OHP-based adjuvant chemotherapy such as FOLFOX or CPT-11 plus infusional leucovorin and fluorouracil (FOLFIRI), three patients received S-1 plus CPT-11, and one patient received best supportive care. At last follow-up, five patients were still receiving chemotherapy.

Table 2. Characteristics of patients with disease recurrence (median follow-up period, 70 months [range, 9–120 months])

Case	Sex	Age (years)	Location	Operation	Histologic type	Depth of tumor	Stage	No. of LNs examined (N)	Site of recurrence
1	Male	71	A	Elective	tubular	T3	IIa	10	Lung
2	Female	52	A	Emergency	tubular	T4b	IIc	25	Anastomosis
3	Female	55	S	Emergency	tubular	T4a	IIIb	4	Cervical lymph node
4	Female	70	S	Elective	tubular	T4b	IIIc	8	Liver
5	Male	76	A	Elective	tubular	T4b	IIc	41	Anastomosis
6	Female	56	D	Elective	tubular	T3	IIa	9	Lung
7	Male	62	D	Elective	tubular	T3	IIa	5	Omentum
8	Female	80	C	Elective	tubular	T4b	IIIc	22	Peritoneum
9	Female	77	RS	Elective	tubular	T3	IIIb	17	Liver
10	Male	73	D	Elective	tubular	T4a	IIb	11	Anastomosis
11	Female	54	Rb	Elective	tubular	T3	IIa	20	Lung
12	Male	65	Ra	Elective	tubular	T4a	IIIa	12	Peritoneum
13	Male	58	Rb	Elective	tubular	T3	IIIa	28	Anastomosis
14	Male	49	C	Elective	mucinous	T4a	IIb	50	Mediastinal lymph node
15	Male	64	C	Elective	tubular	T4a	IIIb	24	Liver
16	Male	73	S	Elective	tubular	T4b	IIc	12	Anastomosis
17	Female	57	S	Elective	tubular	T4a	IIIb	19	Peritoneum

	Treatment for recurrence	Time to relapse (M)	Over all Survival (M)	Prognosis
1	Operation → S-1 / CPT11 → Bev. / FOLFOX → Operation → Bev. / FOLFIRI → BSC	15.1	90	Unknown
2	FOLFOX → BSC	6.8	12	Death
3	Bev.FOLFIRI (Ongoing)	78	114	Survival
4	Operation → Bev. / FOLFIRI → BSC	6.8	53	Death
5	Operation → BSC	17	31	Death
6	Operation → Bev. / FOLFOX → BevFOLFIRI → Cetuximab (Ongoing)	36.5	98	Survival
7	Operation → Bev. / FOLFOX → Bev. / FOLFIRI → Cetuximab (Ongoing)	27.3	96	Survival
8	Not chemotherapy (BSC)	26.7	43	Death
9	Operation	8	50	Unknown
10	Operation → Lung metastasis → BSC	35.5	87	Death
11	S-1 / CPT-11 → Bev FOLFOX (Ongoing)	15.1	90	Survival
12	Bev. / FOLFOX → Bev. / FOLFORI → BSC	24.2	38	Death
13	FOLFOX → FOLFIRI	22.3	64	Unknown
14	S-1 / CPT-11 → Bev. / Xelox → Cetuximab / CPT-11 → BSC	12	38	Death
15	S-1 / CPT-11 → Bev. / FOLFOX → BSC	11	22	Death
16	Operation → Capecitabine (Ongoing)	22.1	80	Survival
17	Bev. / FOLFOX → BSC	26.3	53	Unknown

A Ascending colon, *S* Sigmoid colon, *D* Descending colon, *RS* Rectosigmoid, *Ra* Rectum (above the peritoneal reflection), *Rb* Rectum (below the peritoneal reflection), *M* Months, *FOLFOX* Oxaliplatin plus infusional leucovorin and fluorouracil, *FOLFIRI* CPT-11 plus infusional leucovorin and fluorouracil, *Bev*. Bevacizumab, *BSC* Best supportive care

At the time of the final analysis, eight patients (8.7%) had died due to disease progression. The 5-year DFS and OS rates for the entire study population were 82.2% and 91.9%, respectively (Fig. 1a, b).

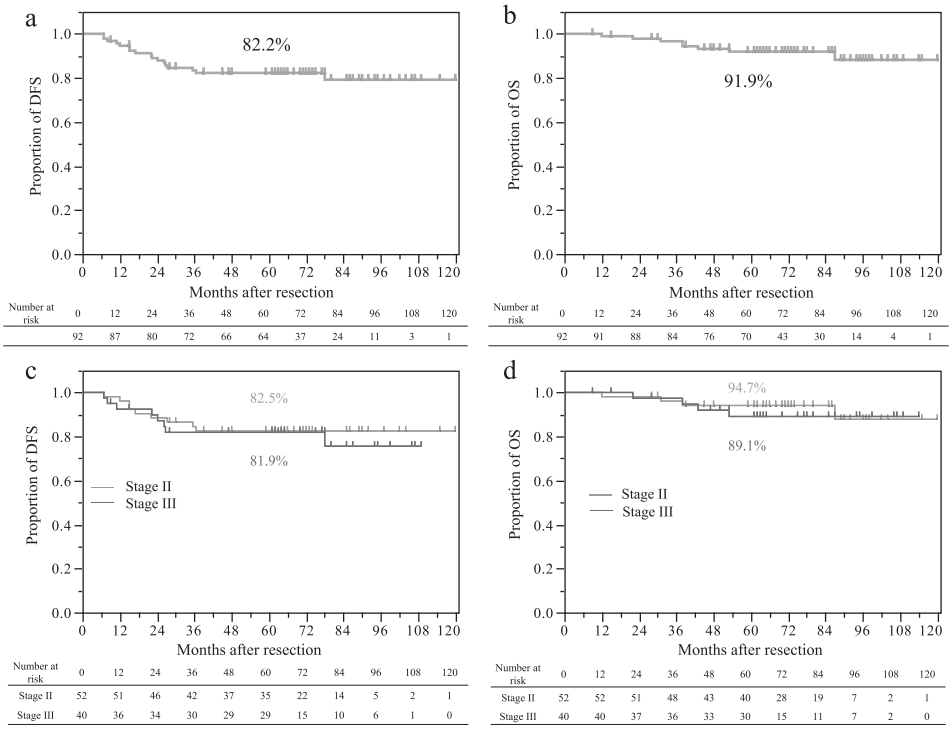


Fig. 1. Disease-free survival (DFS) and overall survival (OS) curves for all patients and for patients in Stage II and III.
(a) DFS curve for all patients; the 5-year DFS rate was 82.2%.
(b) OS curve for all patients; the 5-year OS rate was 91.9%.
(c) DFS curves for Stage II and Stage III patients; the 5-year DFS rates for Stage II and Stage III patients were 82.5% and 81.9%, respectively. There was no significant difference in 5-year DFS between Stage II and Stage III patients (log-rank test; $p = 0.696$).
(d) OS curves for Stage II and Stage III patients; the 5-year OS rates for Stage II and Stage III patients were 94.7% and 89.1%, respectively. There was no significant difference in 5-year OS between Stage II and Stage III patients (log-rank test; $p = 0.674$).

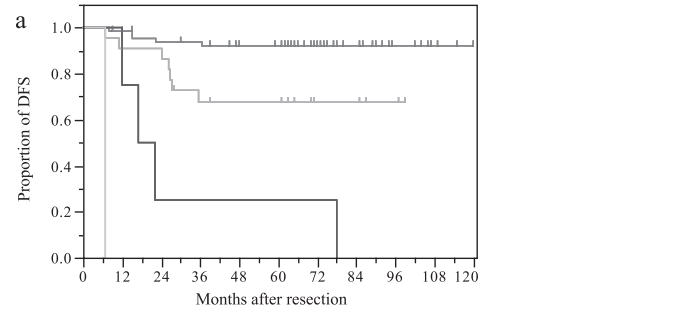
Prognostic factors for recurrence

Results of the univariate and multivariate analyses using the Cox proportional hazard model to identify significant prognostic factors for recurrence are presented in Table 3. In the univariate analysis, five variables were identified as significant prognostic factors for recurrence affecting DFS: preoperative CA19-9 level >37 U/ml (hazard ratio [HR], 6.520; 95% CI, 1.961–19.650; $p = 0.0036$), emergency operation (HR, 8.978; 95% CI, 1.404–32.284; $p = 0.025$), D1 LN dissection (HR, 6.977; 95% CI, 1.093–25.034; $p = 0.042$), T4 lesions (HR, 7.553; 95% CI, 2.860–22.015; $p < 0.0001$), and >3 LN metastases (HR, 5.661; 95% CI, 1.296–17.570; $p = 0.025$). In the multivariate analysis, preoperative CA19-9 level >37 U/ml (HR, 7.826; 95% CI, 1.562–33.271; $p = 0.016$), emergency operation (HR, 3.560e+9; 95% CI, 1.323–1.164e+20; $p = 0.038$), and T4 lesions (HR, 5.571; 95% CI, 1.472–22.184; $p = 0.012$) were independent significant prognostic factors after treatment. Both DFS and OS were significantly different according to the number of independent prognostic factors for recurrence (number of prognostic factors 0 vs ≥ 1: HR,

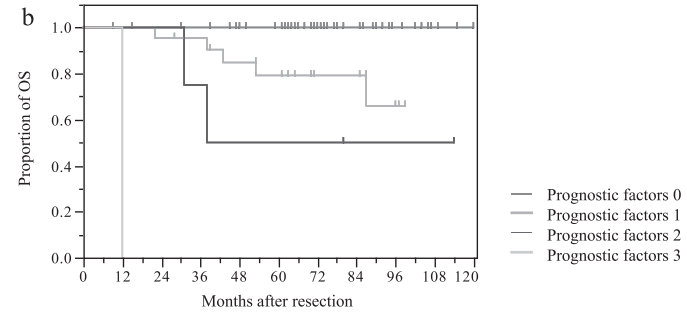
Table 3. Univariate and multivariate analyses using the Cox proportional hazard model to identify significant prognostic factors for recurrence

	Univariate analysis		Multivariate analysis	
Factor	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (years)				
＞65	0.639 (0.232-1.667)	0.36		
≦65	1			
Sex				
Male	0.584 (0.223-1.556)	0.274		
Female	1			
Preoperative CEA level (ng / ml)				
＞5.1	1.312 (0.422-3.952)	0.627		
≦5.1	1			
Preoperative CA19-9 level (U / ml)				
＞37	6.520 (1.961-19.650)	0.0036	11.038 (2.517-47.262)	0.0025
≦37	1		1	
Operation				
Emergency	8.978 (1.404-32.284)	0.025	15.002 (1.732-101.219)	0.017
Elective	1		1	
Tumor location				
Colon	2.561 (0.905-9.102)	0.078		
Rectum	1			
Surgical approach				
Laparotomy	1.792 (0.663-6.640)	0.258		
Laparoscopic	1			
Tumor size				
＞50	0.783 (0.284-2.040)	0.618		
≦50	1			
LN dissection				
D1	6.977 (1.093-25.034)	0.042	2.058 (0.088-23.763)	0.592
D2, D3	1		1	
Histologic types				
Mucinous, poorly	1.695 (0.266-6.070)	0.513		
Tubular, Papirally	1			
Depth of tumor				
T4	7.553 (2.860-22.015)	＜0.0001	4.956 (1.172-21.230)	0.03
≦T3	1		1	
Lymphatic invasion				
Positive	1.053 (0.297-2.977)	0.928		
Negative	1			
Venous invasion				
Positive	1.539 (0.434-9.767)	0.545		
Negative	1			
No. of LNs examined				
＞13	1.952 (0.733-5.107)	0.175		
≦13	1			
No. of LN metastases				
＞3	5.661 (1.296-17.570)	0.025	4.101 (0.572-19.610)	0.14
≦3	1		1	
Stage				
II	1.208 (0.453-3.162)	0.698		
III	1			
Postoperative complications				
＋	1.948 (0.676-5.131)	0.207		
－	1			

CEA Carcinoembryonic antigen, *CA19-9* Carbohydrate antigen 19-9



Number at risk	0	12	24	36	48	60	72	84	96	108	120
0	65	63	59	58	53	52	31	19	8	3	1
1	22	20	20	13	11	11	5	4	3	0	0
2	4	4	1	1	1	1	1	0	0	0	0
3	1	0	0	0	0	0	0	0	0	0	0



Number at risk	0	12	24	36	48	60	72	84	96	108	120
0	65	64	63	62	58	56	39	35	9	3	1
1	22	22	21	19	15	13	7	7	4	0	0
2	4	4	4	3	2	2	2	1	1	1	0
3	1	1	0	0	0	0	0	0	0	0	0

Fig. 2. Disease-free survival (DFS) and overall survival (OS) curves based on the number of prognostic factors for recurrence.*

(a) DFS curves based on the number of prognostic factors for recurrence

(b) OS curves based on the number of prognostic factors for recurrence

* Number of prognostic factors 0 vs >1: hazard ratio, 6.976; 95% CI, 2.580–21.973; log-rank test, $p<0.0001$; Wilcoxon test, $p<0.0001$.

6.976; 95% CI, 2.580–21.973; log-rank test, $p < 0.0001$; Wilcoxon test, $p < 0.0001$) (Fig. 2).

Discussion

To our knowledge, this is the first report on the analysis of prognostic factors for recurrence after UFT / LV adjuvant chemotherapy for patients with CRC. In this study, common sites of recurrence after UFT / LV adjuvant chemotherapy included the anastomosis (29.4% [5 / 17]), and other local sites, the liver and the lungs (17.6% [3 / 17] each). According to the JSCCR, the recurrence rates after curative resection are 2.4% for the anastomosis, 23.1% for other local

sites, 41.2% for the liver, 27.6% for the lungs, and 22.0% for other sites (including overlaps)[6]. Although it is not possible to directly compare recurrence patterns, they may have been affected by UFT / LV adjuvant chemotherapy; in particular, hematogenous metastases such as liver and lung metastases may have been suppressed by UFT / LV.

In NSABP C-06, which evaluated the non-inferiority of UFT / LV compared with intravenous 5-FU / levofolinate (l-LV) as adjuvant chemotherapy in Stage II and III colon cancer, the 5-year DFS rate was 67.0%[3]. Conversely, in JCOG0205, which also evaluated the non-inferiority of UFT / LV compared with 5FU / l-LV in Stage III CRC, the 5-year DFS rate was 73.6%. In our study, the 5-year DFS rate was 82.2% for all patients and 81.9% for patients in Stage III (Fig. 1c)[2]. The 5-year OS rate for patients in Stage III in our study was 89.1% (Fig. 1d), which was similar to the 87.5% in the JCOG0205 trial. In our study, 16 of the 17 patients who had recurrence underwent surgery or systemic chemotherapy for recurrence, and five received L-OHP- or 5FU-based chemotherapy during progression-free survival. Thus, in addition to the UFT / LV adjuvant chemotherapy, surgery and novel anticancer agents may have contributed to the remarkable improvement in the 5-year OS.

The pathological stage of T4 and intestinal perforation can identify a minority of Stage II CRC patients who have a higher risk of recurrence[8-10]. Of the 17 patients who had recurrence after UFT / LV adjuvant chemotherapy in our study, nine were in Stage II (Table 2). Of them, five had T4 lesions, and three had <13 sampled LNs. This meant that eight of the nine Stage II patients who had recurrence (88.9%) had high-risk Stage II disease. Therefore, aggressive adjuvant chemotherapy should given to patients with CRC who are in Stage III and to a minority of those in high-risk Stage II.

Serum CEA levels have been shown to be elevated in a majority of patients with recurrence after curative resection for CRC[14]. In particular, 80% of patients with hepatic recurrence had elevated serum CEA levels. In this study, the preoperative CEA level was not a significant prognostic factor for recurrence after UFT / LV adjuvant chemotherapy in the univariate analysis. The UFT / LV adjuvant chemotherapy may have suppressed hematogenous metastases such as liver and lung metastases; as a result, preoperative CEA level was not selected as a prognostic factor for recurrence. Although the American Society of Clinical Oncology guidelines for the use of tumor markers in CRC state that there are insufficient data to recommend CA19-9 for screening, diagnosis, staging, surveillance, or treatment monitoring in CRC[15], CA19-9 has been widely used as a tumor marker for CRC. Takakura *et al* reported that the preoperative CA19-9 level was a significant predictor of peritoneal dissemination and poor survival in patients with CRC[16]. Furthermore, Nakagoe *et al* reported that the preoperative CA19-9 level might serve as a useful marker in identifying node-negative CRC patients who are at high risk of recurrence after surgery[17]. Since recurrence patterns may have changed with UFT / LV adjuvant chemotherapy and the rate of peritoneal recurrence was high, we selected the preoperative CA19-9 level (which is a significant predictor of peritoneum recurrence) as an independent prognostic factor for recurrence.

The 5-year DFS and OS rates for patients who had at least one of the independent

prognostic factors (T4 lesions, emergency operation, and high preoperative CA19-9 level) were significantly worse than those for patients who did not have any of these three factors. Therefore, Stage Ⅲ or high-risk Stage Ⅱ CRC patients with none of the three independent prognostic factors may be suitable for oral 5-FU-based adjuvant chemotherapy. Stage Ⅲ or high-risk Stage Ⅱ patients who have any one of three independent prognostic factors should receive another recommended adjuvant therapy, such as L-OHP-based chemotherapy, because they have a very high likelihood of recurrence.

Several limitations to our study must be considered. First, the number of patients was small. This meant that while emergency operation was selected as an independent prognostic factor, only two patients had emergency operations in our study. Therefore, type I errors could not be avoided when analyzing prognostic factors for recurrence. However, CRC with perforation was not found to be an independent prognostic factor in our study, although it has previously been shown to be a risk factor for recurrence and to indicate poor prognosis[18-20], so it must be an important prognostic factor. Second, we conducted a retrospective study at a single institution, not a prospective study that compared CRC patients with and without adjuvant therapy. Third, our study did not include the biomarkers associated with CRC recurrence or molecular markers associated with response to anticancer agents. Several molecular markers have been shown to be satisfactory predictors of the efficacy of 5-FU-based or L-OHP-based chemotherapy[21-27]. Yothers *et al* reported that the 12-gene Recurrence Score provides additional information beyond the conventional clinical and pathological factors[28]; this score is a predictor of recurrence risk that was developed using gene expression data[29]. In clinical practice, these factors could improve decision-making regarding adjuvant chemotherapy for patients with Stage Ⅱ and Ⅲ colon cancer.

In conclusion, for patients with CRC who receive UFT / LV adjuvant chemotherapy, three independent prognostic factors — T4 lesions, emergency operation, and a high preoperative CA19-9 level — may be useful for decision-making regarding the choice between 5-FU-based and L-OHP-based adjuvant chemotherapy.

Conflict of interest disclosure

We have no conflicts of interest to declare.

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