Postoperative Chemotherapy for Colorectal Cancer by Combining 5-Fluorouracil Infusion and 1-Hexylcarbamoyl-5-Fluorouracil Administration after Curative Resection

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BACKGROUND. Colorectal cancer is one of the major malignant diseases and, recently, its incidence appears to be increasing. Surgical resectability is an important prognostic determinant; however, recurrent tumors are commonly noted, even after apparently curative surgery. Because such metastatic disease cannot be cured, better adjuvant therapies are urgently called for.

METHODS. We studied the effect of postoperative chemotherapy using 5-fluorouracil (5-FU) infusions and 1-hexylcarbamoyl-5-fluorouracil (HCFU) oral administration for curatively resected Stage II to IV colorectal cancer. This study was prospectively randomized and controlled and 251 (93.3%) of 269 patients were determined to be candidates for statistical assessment. The inductive regimen for Group A included a total of 6 5-FU intravenous injections, 10 mg/kg, on postoperative days 0, 1, 2, 7, 8, and 9. For maintenance therapy, Group A also received oral HCFU, 300 mg daily for 52 weeks beginning 2 weeks after surgery. The regimen for Group B included only 5-FU injections of Group A.

RESULTS. There were no differences in the prognostic factors or doses of 5-FU between Groups A and B. In addition, no difference was observed in the toxicity rate between the two groups. Group A, with 5-FU infusions plus oral HCFU administration, produced a reduction in the recurrence rate and a prolongation of the survival time for patients with rectal cancer. In a retrospective analysis, this protocol was also effective for patients with Stage III to IV, wall invasion-positive, and lymph node metastasis-positive colorectal cancers.

CONCLUSIONS. This study suggests that the combination of 5-FU infusions and the continuous oral administration of HCFU is a reasonable therapeutic approach for patients with surgically resected colorectal cancer and a high risk of recurrence.
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KEYWORDS: colorectal cancer, postoperative chemotherapy, 5-fluorouracil, 1-hexylcarbamoyl-5-fluorouracil, recurrence, prognosis.

After curative resection of tumors in the colon and rectum, various types of recurrence occur due to the presence of residual occult disease and distant micrometastasis.[1,2] As a result, there is great interest in developing an adjuvant treatment that will improve the prognosis in these patients. There have been trials of adjuvant chemotherapy for colorectal cancers; however, the majority of these studies failed to show any significant advantage in the various adjuvant therapies over observation. However, Moertel et al. did show an unequivocally significant advantage in treatment with 5-fluorouracil (5-FU) plus levamisole on surgically resected colon cancer in Dukes' Stage C.[3] Another study also reported the

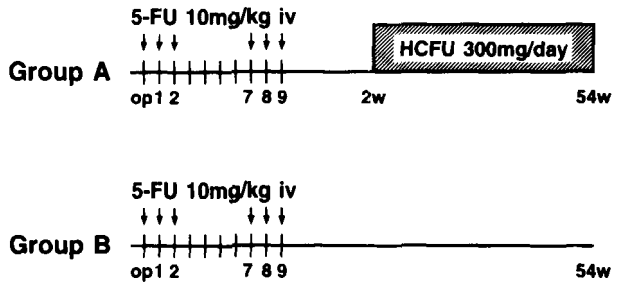

FIGURE 1. Schedule for the administration of chemotherapy.

advantage of portal-vein adjuvant therapy.[4] O'Connell et al. reported that a protracted infusion of 5-FU during pelvic irradiation improved survival in patients with rectal cancer.[5] Thus, 5-FU is currently the most active drug available for such diseases.

One of the major problems in the treatment of colorectal cancers is chemoresistance.[6] 1-hexylcarbamoyl-5-fluorouracil (HCFU) was developed by Hoshi et al.[7,8] in 1975 as a lipophilic masked compound of 5-FU for oral use and has been prescribed in Japan since 1980. HCFU is converted to 5-FU either enzymatically or nonenzymatically,[9–11] and oral HCFU has both a higher therapeutic ratio and a wider tumor spectrum than 5-FU in a variety of experimentally induced tumors.[12,13] HCFU is used to treat patients with various solid tumors, including gastrointestinal cancers.[14–16] We found HCFU to be more effective for colorectal cancer tissue specimens in vitro compared with 5-FU, based on the chemosensitivity test.[17,18] In colorectal cancer cases, the response rate was 15% for 5-FU[19,20] and 11% for tegafur.[21] The Phase II study for HCFU revealed a 43% response rate in colorectal cancers,[15] thereby suggesting that HCFU is an effective drug in the 5-FU family with regard to colorectal cancers. Niimoto et al. found that patients with a noncuratively resected colorectal cancer responded to the postoperative chemotherapy of mitomycin C and HCFU, in comparison with the findings with mitomycin C alone, in particular for cases with liver metastasis or peritoneal dissemination.[22]

We thus began a randomized study to evaluate the effect of HCFU as an adjuvant chemotherapy for patients with colorectal cancer who underwent curative resection.

PATIENTS AND METHODS

Patients

All patients included in the prospectively randomized and controlled trial underwent a macroscopic curative resection for colorectal cancer. The 269 patients were entered into this study between July 1989 and June 1991. The patients were assigned, at random, to either Group A or B on the day of surgery. The protocol was as follows (Fig. 1): the inductive regimen for Group A included 10 mg/kg intravenous drip infusions of 5-FU (Kyowa Hakko Co., Tokyo) on postoperative days 0, 1, 2, 7, 8, and 9. For maintenance therapy, Group A received orally 300 mg of HCFU (Mitsui Pharmaceutical Inc., Tokyo) daily beginning 2 weeks after the operation for 52 weeks. The regimen for Group B included only the 5-FU injections as received by Group A. The patients were selected on the basis of: (1) a histologic diagnosis of colorectal cancer; (2) a macroscopic Stage of II–IV; (3) a macroscopic diagnosis as a curative case, on completion of the surgical procedures; (4) an age of less than 76 years; (5) a performance status Grade of 0–2; (6) no evident synchronous or metachronous double cancer; and (7) an adequate organ system function (leukocyte count of $>4{,}000\ mm^{-3}$; platelet count of $>100{,}000^{-3}$; and glutamic-oxaloacetic transaminase and glutamic pyruvic transaminase levels of <100 U). The pathologic diagnosis and classifications were evaluated according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus in Japan (Table 1).[23] Lymph nodes in Groups 1, 2, and 3 are referred to as n1, n2, and n3, respectively, and the distant lymph nodes located beyond Group 3 (n3) are referred to as n4. Colorectal resection based on lymph node dissection was classified as follows: R0, colorectal resection including the incomplete removal of Group 1 lymph nodes; R1, colorectal resection including the complete removal of Group 1 lymph nodes alone; R2, colorectal resection including the complete removal of Group 1 and 2 lymph nodes; and R3, colorectal resection including the complete removal of Group 1, 2, and 3 lymph nodes.

Statistical Analysis

The data were analyzed using the chi-square test, Mann–Whitney U test, and Student's t test. The survival curves were calculated by the Kaplan–Meier method. Comparisons were made by the log rank test. A P value of less than 0.05 was considered to be significant.

RESULTS

Of the 269 patients, 18 (6.7%) had to be excluded: 1 had no cancer, 1 had double cancers, 2 had multiple cancers, 1 was over 76 years of age at operation, 3 were treated for a noncurative resection macroscopically, and 10 had macroscopic Stage I cancer. The patients were followed in the outpatient department at 2-week intervals. Attention was directed to their general condition, bone marrow function, liver function, and serum carcinoembryonic antigen levels, and imagings were taken at 6-month intervals.

Clinicopathologic Features

Clinicopathologic details of the 251 eligible cases (93.3%) of 142 colon cancers and 109 rectal cancers were as fol-

TABLE I
Histological Staging According to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus in Japan

	Factor				
Stage	Depth of "invasion"	Lymph node "metastasis"	Peritoneal "dissemination"	Liver "metastasis"	Distant "metastasis"
I	m, sm, pm	n(−)	(−)	(−)	(−)
II	ss, s, a1*, a2*	n(−)	(−)	(−)	(−)
III	si ai*	n1(+)	(−)	(−)	(−)
IV	si ai*	n2(+), n3(+)	(−)	(−)	(−)
V	si ai*	n4(+)	(+)	(+)	(+)

m: mucosa; sm: submucosa; pm: muscularis propria; ss: subserosa; s: serosa; si: serosa (infiltrating adjacent organs); a1: beyond muscularis propria but does not penetrate deeper; a2: beyond muscularis propria infiltrating deeper but not infiltrating adjacent organs; ai: infiltrating adjacent organs.
*Site without serosa.

lows: In the colon cancer cases, there were 71 patients in Group A, and 71 patients in Group B, and in the rectal cancer cases, there were 55 patients in Group A and 54 patients in Group B (Table 2). There were no significant differences between the groups with regard to the distribution of prognostic factors in colon and rectal cancers.

Doses of Drugs

There was no difference in the 5-FU dose between the groups. HCFU was prescribed at the total dose of 90.5 ± 38.1 g for Group A in the colon cancer cases and at 74.0 ± 41.3 g for Group B in the rectal cancer cases (Table 3).

Survival Rates

Figure 2 shows the survival curves of Groups A and B for colon and rectal cancers. The overall survival differed significantly between the rectal cancer treatment groups ($P < 0.05$), whereas no such difference was seen in the colon cancer groups. The 5-year survival rate was 83.3% for Group A and 52.5% for Group B.

We stratified the survival data retrospectively by Stage, wall invasion, and lymph node metastasis in a group of colorectal cancer patients (Figs. 3–5). The protocol of Group A was effective for patients with Stage III–IV (Fig. 3), wall invasion-positive (Fig. 4), or lymph node metastasis-positive colorectal cancers (Fig. 5), with statistical significances ($P < 0.05$).

When we analyzed the patients at high risk for recurrence of Stage III–IV, wall invasion-positive, and lymph node metastasis-positive colorectal cancers in each of the groups, the five-year survival rate was higher in Group A compared with that in Group B (Table 4). Significant differences were noted for Stage III–IV and lymph node metastasis-positive rectal cancer.

Recurrences

The data for patients who underwent a curative resection histologically were examined regarding the rate and style of recurrence (Table 5). In the rectal cancer cases, the recurrence rate decreased prominently ($P < 0.05$), particularly for liver recurrence in Group A compared with Group B. In the colon cancer cases, no difference in the rate or the style of recurrence was observed between the Groups A and B.

Toxicities

Table 6 summarizes the factors related to toxicity. Various side effects occurred in each group, as did hematologic toxicities. The rates of heat sensation, pollakiuria, and specific toxicities of HCFU were low for the HCFU-prescribed group, and there was no difference between the groups regarding colon and rectal cancers.

DISCUSSION

Colorectal cancer is one of the most serious diseases of our time. Although complete remission has been achieved in some cases, the disease always recurred during the long term follow-up.[1,2] There is great interest in developing adjuvant therapies that will improve the disease free interval and survival in these patients. A prospective randomized clinical study showed that the combined administration of mitomycin C and HCFU is a safe and effective adjuvant chemotherapy for noncuratively resected patients with colorectal cancer.[22] In this article, we examined the adjuvant effect of HCFU on colorectal cancer following a curative resection.

The rate of recurrence decreased, especially for liver recurrence in rectal cancer, in the group treated with 5-FU plus oral administration of HCFU, and the survival rate also improved, in particular in advanced cases. The continuous administration of HCFU was intended to prolong the exposure of tumor cells to 5-FU, and, therefore, the prolonged maintenance of the blood 5-FU level resulted in an improved systemic effect on micrometastasis

TABLE 2
Comparison of the Clinicopathologic Characteristics Between the Patients in Groups A and B

		Colon			Rectum		
Factor	Category	Group A (n = 71)	Group B (n = 71)	*P* value	Group A (n = 55)	Group B (n = 54)	*P* value
Sex	Male	35	30	NS	34	28	NS
	Female	36	41		21	26	
Age (yrs)	~39	3	1	NS	2	1	NS
	40~49	4	6		6	1	
	50~59	18	22		18	15	
	60~69	31	24	NS	21	29	NS
	70~75	15	18		8	8	
Macroscopic Stage	II	23	14		23	18	
	III	29	35		19	23	
	IV	19	22	NS	13	13	NS
Histologic Stage	I	6	6		9	12	
	II	34	35		22	22	
	III	19	18		17	12	
	IV	11	11		6	7	
	V	1	0		0	1	
	Unknown*	0	1	NS	1	0	NS
Histological tumor invasion through the colorectal wall*	Negative	47	45	NS	37	38	NS
	Positive	24	26		17	16	
	Unknown†	0	0		1	0	
Histological lymph node metastasis	Negative	41	43	NS	32	34	NS
	Positive	30	27		22	20	
	Unknown†	0	1		1	0	
Lymph node dissection	R0 & R1	4	3	NS	4	4	NS
	R2 & R3	67	68		51	50	
Histological curability	Curative	70	70	NS	53	52	NS
	Noncurative	1	0		1	2	
	Unknown†	0	1		1	0	

NS: nost significant; RO: colorectal resection including the incomplete removal of Group 1 lymph nodes; R1: colorectal resection including the removal of Group 1 lymph nodes alone; R2: colorectal resection including the complete removal of Group 1 and 2 lymph nodes; R3: colorectal resection including the complete removal of Group 1, 2, and 3 lymph nodes.

* Negative means the depth of invasion of mucosa; submucosa; muscularis propria; subserosa; or beyond the muscularis propria without penetrating deeper; and positive do serosa, serosa infiltrating adjacent organs; beyond muscularis propria, infiltrating deeper but not infiltrating adjacent organs; or infiltrating adjacent organs.

† All unknown cases were excluded in the statistical analysis.

TABLE 3
Drug Dosage

	Colon cancer		Rectal cancer	
Drug	Group A (n = 71)	Group B (n = 71)	Group A (n = 55)	Group B (n = 54)
Total dose of "5-FU (mg)"	2980 ± 590	2910 ± 600	2820 ± 760	2820 ± 890
Total dose of "HCFU (g)"	90.5 ± 38.1	-	74.0 ± 41.3	-
Prescription of "HCFU (days)"	293 ± 121	-	250 ± 137	-

5-FU: 5-fluorouracil; HCFU: 1-hexylcarbamoyl-5-fluorouracil.

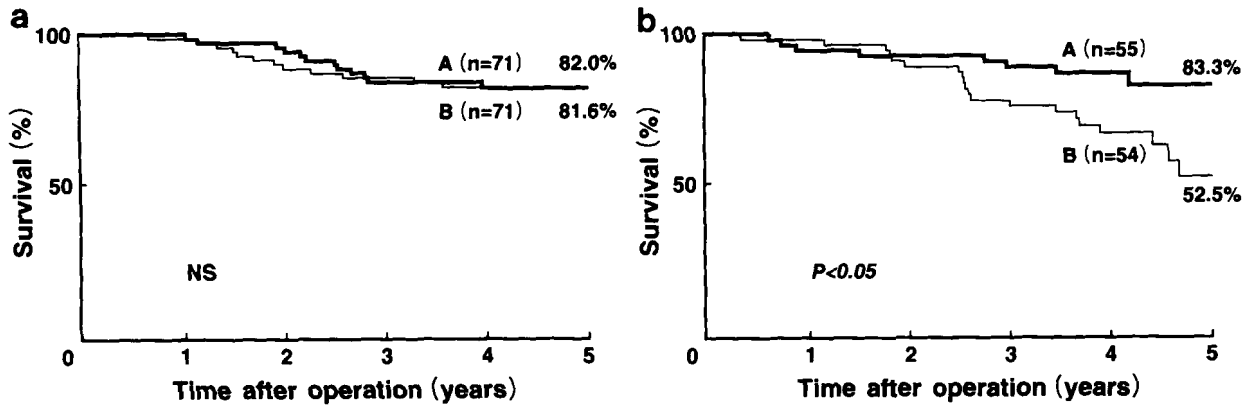

FIGURE 2. Survival curves for Groups A and B regarding colon and rectal cancers. An improvement in the survival time was noted in Group A compared with that in Group B for rectal cancer (b), with a statistical difference ($P < 0.05$), and there was no difference between the groups with colon cancer (a). Group A: solid line; Group B: light line.

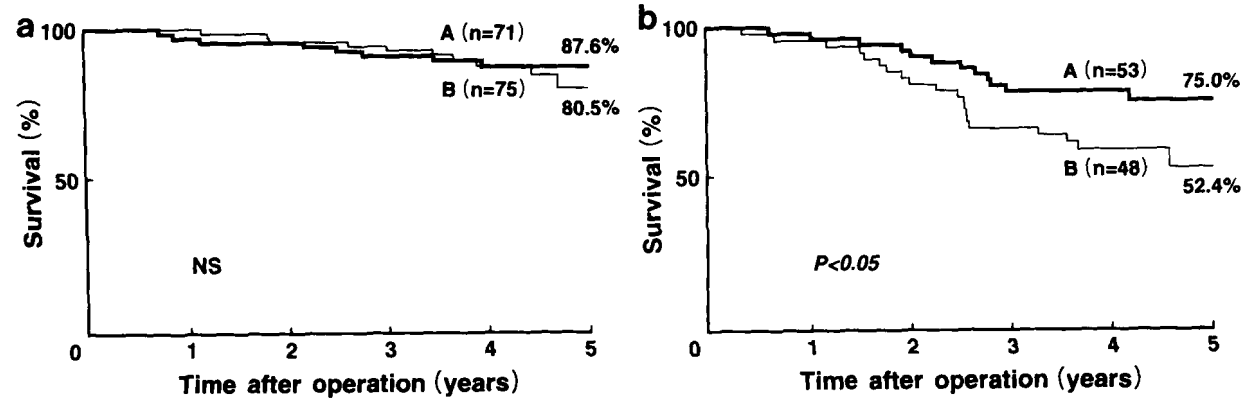

FIGURE 3. Survival curves for groups A and B regarding Stage I–II and Stage III–IV colorectal cancers. An improvement in the survival time was noted in Group A for stage III–IV, with a statistical difference ($P < 0.05$), and there was no difference for Stage I–II.

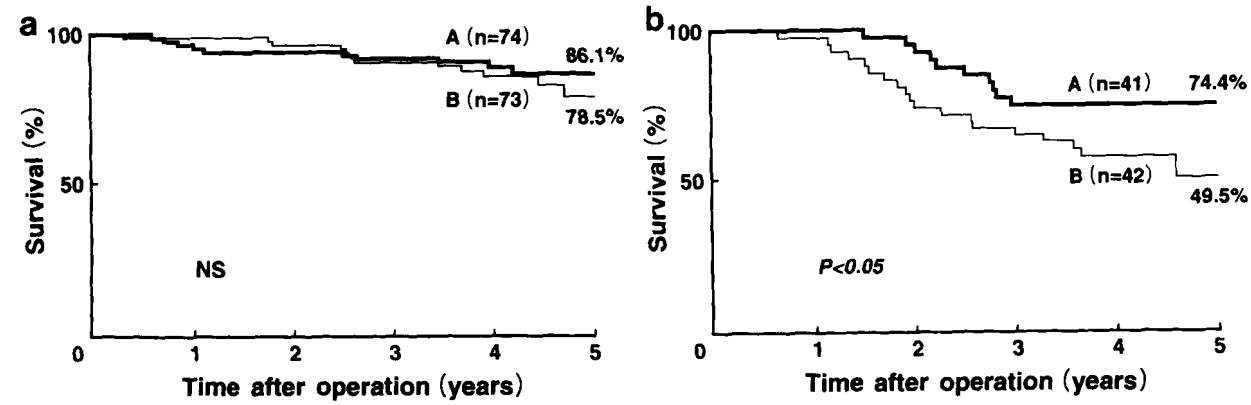

FIGURE 4. Survival curves for groups A and B regarding wall invasion-negative and -positive colorectal cancers. An improvement in the survival time was noted in Group A for wall invasion-positive colorectal cancers ($P < 0.05$) (b), and there was no difference for wall invasion-negative cancers (a).

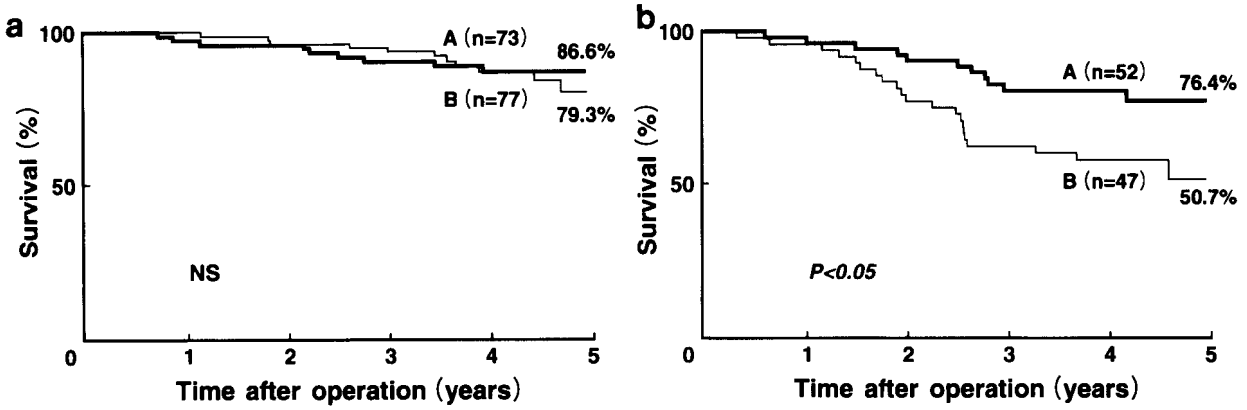

FIGURE 5. Survival curves for Groups A and B regarding lymph node metastasis-negative and -positive colorectal cancers. An improvement in the survival was noted in Group A for lymph node metastasis-positive colorectal cancers ($P < 0.05$) (b), and there was no difference for node-negative cancers (a).

TABLE 4
Five-Year Survival for Groups A and B in Patients with Colorectal Cancer and High Risk of Recurrence

Factor	Group	5-year survival (%)	
Stage III-IV			
Colon cancer	A (n = 30)	72.0	
	B (n = 28)	58.4	
Rectal cancer	A (n = 23)	78.1	$P< 0.05$
	B (n = 20)	44.3	
Wall invasion-positive			
Colon cancer	A (n = 24)	70.8	
	B (n = 26)	53.8	
Rectal cancer	A (n = 17)	80.4	
	B (n = 16)	40.1	
Lymph node metastasis-positive			
Colon cancer	A (n = 30)	75.4	
	B (n = 27)	57.7	
Rectal cancer	A (n = 22)	76.6	$P< 0.05$
	B (n = 20)	42.2	

for rectal cancer. When HCFU was prescribed orally to rodents and humans, both HCFU and 5-FU were transferred to the liver from the stomach via the portal vein.[24,25] Higher levels of HCFU and 5-FU in the portal vein were noted in patients with gastrointestinal malignancy.[26] Iigo et al reported that the hexylcarbamoyl structures facilitate rapid absorption through the gastrointestinal tract and blood-ascites barrier.[27] The chemical structures of HCFU are related to the rapid uptake of HCFU through the cell membrane. HCFU has a higher cytotoxic activity against human tumor cells,[28] and thus HCFU given orally has a higher therapeutic ratio. These pharmacological characteristics of HCFU are considered to help in suppressing the effect of recurrence in rectal cancer.

Local recurrence is another type of recurrence in rectal cancer.[1,2] It has been reported that combination postoperative local therapy with radiation plus chemotherapy decreased local recurrence.[5,29] We also found preoperative hyperthermochemoradiotherapy, including HCFU administration, to be effective for preventing tumor cell spread during surgical procedures as well as local pelvic recurrence in rectal cancer.[30,31] Therefore, a combination of local therapy with radiation and hyperthermia is considered to be one approach for improving the effect of HCFU in patients with rectal cancer.

In this study, we found no significant effect of HCFU on patients with colon cancer, but the prognosis was somewhat better in both Groups A and B. Other studies indicated that the outcome of surgery for high risk colon cancer of Dukes' Stage C is significantly improved by the use of 5-FU in combination with levamisole[3] or folinic acid.[32,33] A retrospective analysis showed that our protocol is effective for a subset of patients with Stage III–IV, wall invasion-positive, and lymph node metastasis-positive colorectal cancers. Therefore, this combined treatment of 5-FU and HCFU may be a viable approach for patients with a high risk of recurrence of colorectal cancer. Moreover, a subset of patients in the high risk groups suitable for the prescription of HCFU may be determined by using the chemosensitivity test.[17,28,34]

5-FU is toxic to cerebellar tissue[35,36] and HCFU may have an increased cerebellar toxicity compared with 5-FU. A Phase I study of HCFU revealed that the toxic effects specific for this drug are transient heat sensations and pollakiuria.[37] However, we observed such side effects only rarely and the patients all seemed to tolerate the treatment of 300 mg daily oral doses of HCFU for 1 year postoperatively.

Our findings show that the combined treatment of 5-FU and HCFU is safe and effective for colorectal cancer,

TABLE 5
Recurrence After a Curative Resection for Colorectal Cancer

	Colon cancer			Rectal cancer		
Factor	Group A (n = 70)	Group B (n = 71)	*P* value	Group A (n = 54)	Group B (n = 52)	*P* value
Without recurrence	55	55	NS	42	31	$P< 0.05$
With recurrence	15	16		12	21	
Local	3	3		5	7	
Liver	4	6		5	10	
Lung	0	3		1	2	
Peritoneum	1	1		0	0	
Others	7	3		1	2	

NS: not significant.

TABLE 6
Toxicities

	Colon			Rectum		
Toxicity*	Group A (n = 71)	Group B (n = 71)	*P* value	Group A (n = 55)	Group B (n = 54)	*P* value
Side effects	14.1	5.7	NS	21.8	18.2	NS
Leukopenia	4.2	2.8	NS	9.1	5.5	NS
Hot sensation	2.8	0	NS	1.8	3.6	NS
Pollakisuria	1.4	0	NS	1.8	1.8	NS
Defecation desire	0	0	NS	1.8	3.6	NS
Anorexia	7.0	1.4	NS	1.8	0	NS
Nausea, Vomiting	4.2	0	NS	1.8	0	NS
Diarrhea	1.4	0	NS	5.5	0	NS
Other side effects	4.2	1.4	NS	5.5	0	NS

NS: not significant.
* Values = % of patients fulfilling each criterion for toxicity.

in particular for those patients with a high risk of recurrence following a curative resection. A prospective study based on the node positivity of each patient is now in progress.

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