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Clinical report

Preoperative UFT administration for patients with advanced colorectal cancer—increased uptake of 5-fluorouracil by tumor tissue is a prognostic factor

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The aim of this study was to clarify whether increased 5-fluorouracil (5-FU) uptake by tumor tissue following preoperative UFT administration is a prognostic factor after surgery in colorectal cancer patients. We examined the concentrations of 5-FU in tumor or normal tissue of 96 colorectal cancer patients who received UFT (400 mg/day) orally for 7 days prior to surgery. Patients were divided into two groups with high or low 5-FU concentrations in tumor tissue (defined as higher or lower than the cut-off value, respectively). The cut-off value of 5-FU was established based on the upper limit of the 95% confidence interval of the median of the concentration found in normal tissue (0.106 μg/g). Of the 96 patients, 62 (64.6%) were in the low-5-FU group and 34 (35.4%) in the high-5-FU group. The latter had a more favorable clinical outcome (p=0.0465). Cox regression analysis revealed that two independent variables, stage and 5-FU status in tumor tissue, were significant for prediction of survival. These findings suggest that increased uptake of 5-FU by tumor tissue following preoperative oral administration of UFT is an independent prognostic factor in colorectal cancer patients. This variable needs to be considered in the design of future therapeutic trials. [© 2000 Lippincott Williams & Wilkins.]

Key words: 5-Fluorouracil, colorectal cancer, oral systemic chemotherapy, UFT, uracil, tegafur.

Introduction

Successful surgical excision of colorectal cancer has resulted in a favorable prognosis compared with other gastrointestinal tract cancers. Nonetheless, nearly half of advanced colorectal cancer patients suffer recurrence after curative resection.[1] The major treatment problem in these patients is not the primary tumor, but metastasis, especially systemic metastases developing within a few years after surgery. These recurrences are probably attributable to proliferation of occult metastases already established at the time of surgery.[2] Therefore, not only adequate adjuvant therapy, such as chemotherapy, after resection of the primary tumor, but determination of prognostic factors should be established.

5-Fluorouracil (5-FU) is the basic drug that has proven reliably effective for the treatment of colorectal cancer.[3] High uptake of 5-FU by tumor tissue after administration of 5-FU or 5-FU analogs is essential for an anti-tumor effect. Fujii *et al.* have reported that oral administration of uracil plus tegafur[4,5] (1-(2-tetrahydrofuyl)-5-fluorouracil) at a molar ratio of 4:1 (UFT; Taiho Pharmaceutical, Tokyo, Japan) is more effective than tegafur or 5-FU alone, and that UFT administration results in higher levels of 5-FU, the active substance, in tumor tissues than administration of an equimolar amount of tegafur or 5-FU.[6–8]

Several clinical trials of preoperative administration of 5-FU analog (UFT or tegafur) for patients with colorectal and gastric cancer have been conducted in Japan.[9–14] The purpose of preoperative chemotherapy may include preoperative down-staging for a greater probability of curative surgery, prevention of tumor growth while awaiting surgery, contributing to subsequent favorable outcome.[9] Although these trials failed to reveal any efficacy of preoperative 5-FU analog

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(UFT or tegafur) administration with regard to patient survival, other benefits of preoperative chemotherapy observed clinically and in pathology have been reported. More specifically, preoperative oral administration of UFT has induced objective responses (complete or partial remission) of primary gastric cancer as assessed by endoscopy or upper gastrointestinal series studies and histologically measurable effects, such as necrosis or disappearance of the tumor, or replacement of the tumor by fibrosis.[12,14] Fujii[15] reported that histopathologic assessment following preoperative UFT chemotherapy provides information for prediction of fluoropyrimidine sensitivity.

Based on these observations, we hypothesized that 5-FU uptake by the tumor tissue following preoperative administration of 5-FU analogs (UFT or tegafur) is associated with a clinical and/or histological response of the tumors, and with subsequent patient outcome, because high 5-FU uptake by tumor tissue is essential for the anti-tumor effect. To date, only one report has evaluated the correlation between 5-FU uptake by the primary tumor tissue following preoperative tegafur administration and outcome in advanced gastric cancer patients, but no significant benefit was found.[9] Thus, the role of 5-FU uptake by the tumor tissue following preoperative 5-FU analog administration as a prognostic factor in colorectal cancer patients remains unclear.

In this study, we measured the concentration of 5-FU in primary tumor tissue obtained from colorectal cancer patients who preoperatively received oral UFT and underwent surgical resection. The aim of this study was to clarify the role of 5-FU uptake by tumor tissue as a prognostic factor after surgery in colorectal cancer patients.

Patients and methods

Patients

The current study was performed as part of a multicenter randomized prospective study of adjuvant chemotherapy with UFT and mitomycin C (MMC) for advanced colorectal cancer.[16] One-hundred and twenty-six patients at eight hospitals in Nagasaki, Japan, were enrolled in the study between June 1987 and June 1990. All patients included in this prospective randomized controlled trial underwent colorectal resection The patients were randomly assigned to either Regimen A or Regimen B on the day of surgery. The protocol was as follows. All patients received UFT (400 mg/day) orally for 7 days prior to surgery, and all patients received an inductive regimen of MMC comprising a 20 mg i.v. injection on the day of operation, 10 mg on postoperative day 1 and 6 mg/m^2 body surface area every month thereafter for 1 year. Patients on Regimen B ('MMC+UFT') received oral UFT postoperatively (400 mg daily for 1 year) and patients on Regimen A ('MMC') did not receive UFT postoperatively. Informed consent was obtained from all patients before enrollment in the study. The criteria for patient selection were as follows: (i) histological diagnosis of colorectal cancer, (ii) macroscopic determination of curative or non-curative resection upon completion of the surgical procedure, (iii) maximum age of 76 years, (iv) a performance status grade of 0–3, (v) no evidence of synchronous or metachronous double cancer, and (vi) adequate organ system function (leukocytes >4000 mm^{-3}, platelets $>100\,000$ mm^{-3}, GOT and GPT <80 U, negative urine protein).

The current study included a total of 96 patients out of the 126 colorectal cancer patients enrolled in the randomized trial above. The concentration of 5-FU in two different tissues, primary tumor and normal tissue, was measured in all 96 patients.

Of the 96 patients, 56 were alive at the end of the follow-up period (April 1995). Recurrence of colorectal cancer and death occurred in 34 patients, and six patients died of another disease. The median follow-up period was 1046 days (range 57–1876). The end-point in the current study was the time of death due to colorectal cancer recurrence after surgery. Data from patients who died of causes other than colorectal cancer were censored in the statistical analysis.[17] None of the patients died within 30 days postoperatively.

Histologic analysis

Surgically resected specimens from the 96 colorectal cancer patients were fixed in 10% formaldehyde and embedded in paraffin. Sections were prepared and stained with hematoxylin & eosin. American Joint Committee (AJCC) Classification and Stage grouping were used for tumor assessment.[18] Histological type was determined according to the WHO International Histological Classification of Tumors.[19] Guided by this system, the histologic diagnoses were established by two pathologists. Histologic evidence of invasion beyond the submucosal layer was determined in all specimens. All routine slides were carefully screened to identify venous and lymphatic invasion whenever tumor tissue was detected in veins and lymph vessels, respectively.

All tissue specimens were also evaluated for histologic changes due to preoperative UFT chemotherapy according to the histological criteria of non-surgical treatment for colorectal carcinoma: grade

0 (no change), grade 1 (mild change), grade 2 (moderate change) and grade 3 (severe change).[20]

Determination of the cut-off value for concentration of 5-FU in tumor tissue

The concentration of 5-FU was measured in 0.5–1.0 g specimens of normal and primary tumor tissue using the method described by Marunaka *et al.*[21] Tissue samples were obtained at surgery from the surgical specimens of a total of 96 patients, and were frozen and stored at −80°C until use. The measurement of 5-FU concentration was performed by Taiho Pharmaceutical.

Because the concentrations of 5-FU in the normal tissue did not indicate a normal distribution (Gaussian distribution) as shown in Fig. 1 (Kolmogorov–Smirnov test[22]), the values are reported as medians and ranges within the 95% confidence interval (CI) of the median: median 0.021 μg/g; range 0–0.138 μg/g; 95% CI 0–0.106 μg/g.

In this study, the cut-off value for 5-FU in the tumor tissues is taken as the upper limit of the 95% CI of the median of the concentration in the normal tissue: 0.106 μg/g for 5-FU. We classified the patients into two groups: a high-5-FU group, with 5-FU concentrations in tumor tissue greater than the determined cut-off value, and a low 5-FU group, with less than this value in the tumor tissue.

Statistical analysis

Statistical analyses were performed using the computer program Statistica™ (StatSoft, Tulsa, OK). All tests were two-tailed and a p value of less than 0.05 was considered significant. Results of continuous data are shown as medians and range. Univariate analysis was conducted as follows. Categorical data were analyzed by the χ^2 test or Fisher's exact probability test. Continuous data were analyzed by Mann–Whitney's U-test or Wilcoxon's rank-sum test. Survival was analyzed by the Kaplan–Meier method[23] and differences between the curves were tested by the Wilcoxon test according to Gehan.[24] Multivariate analysis was carried out by the Cox proportional-hazards regression model.[25,26] Factors related to survival were analyzed with the Cox proportional-hazards regression model in a stepwise manner.[25,26] The variables included in Cox's regression analysis were: (i) prognostic factors for colorectal cancer (stage and histologic type) used in patient management and well-supported in the literature;[18] and (ii) potentially prognostic variables identified in the current study.

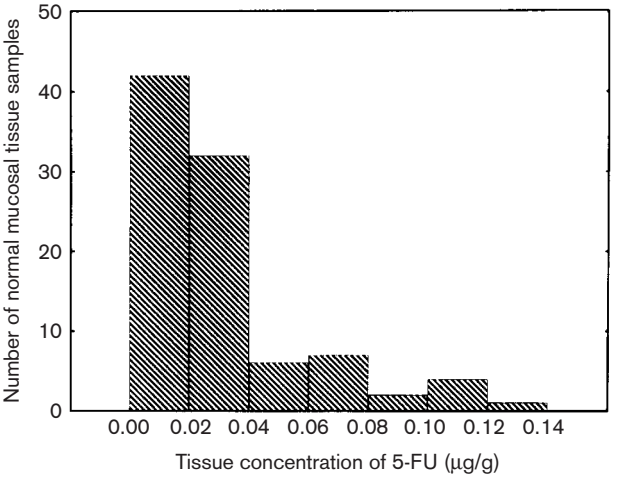

Figure 1. Distribution of concentrations of 5-FU in normal mucosal tissue samples.

Results

Table 1 lists the clinicopathological data of the 96 patients studied. The median of the total preoperative UFT dose per patient was 3.00 (range 1.00–6.00). All patients took the agents completely according to schedule, because no side effects were observed. This resulted in a distribution of 62 patients (64.6%) into the low-5-FU group and 32 (35.4%) in the high-5-FU group.

Histologic response

The resected specimens from all of the 96 colorectal tumors showed neither necrosis nor cellular or structural change throughout the lesion. All resected specimens were therefore judged to be 'grade 0 (no change)' according to the histological criteria of non-surgical treatment for colorectal carcinoma.[20]

Comparison of concentration of 5-FU in normal and tumor tissue

The median and range of 5-FU concentration in the tumor tissue was 0.080 μg/g and 0–0.510 μg/g, respectively. The concentrations of 5-FU in tumor tissue were significantly higher than those in normal tissues ($p < 0.0001$).

Comparison of clinicopathological characteristics in the low 5-FU group and high 5-FU group

As shown in Table 2, there were no significant differences between the low 5-FU group and high 5-

FU group with regard to 11 different pathological variables. Nor were there any significant differences between the low and high 5-FU groups with respect to the total dose of preoperative oral UFT, interval between most recent dose of UFT and operation (Table 2).

Table 1. Clinicopathological characteristics of colorectal cancer patients studied ($n = 96$)

Variable	No. of carcinomas (%)
Age (years)	60, 41–74[a]
Sex	
male	60 (62.5)
female	36 (37.5)
Tumor location	
colon	53 (55.2)
rectum	43 (44.8)
Maximal tumor diameter (cm)	5.5, 2.3–10.0[a]
T	
T2	11 (12.0)
T3	50 (54.3)
T4	31 (33.7)
unknown[b]	4
N	
N0	52 (57.1)
N1/N2	39 (42.9)
unknown[b]	5
M	
M0	88 (91.7)
M1	8 (8.3)
Histologic type	
well differentiated	40 (42.1)
moderately differentiated	48 (50.5)
poorly differentiated/Mucinous	7 (7.4)
unknown[b]	1
Lymphatic invasion	
absent	24 (25.3)
present	71 (74.7)
unknown[b]	1
Venous invasion	
absent	54 (56.8)
present	41 (43.2)
unknown[b]	1
Stage	
I	9 (9.8)
II	38 (41.3)
III	35 (38.0)
IV	10 (10.9)
unknown[b]	4
Concentration of 5-FU in tumor tissue[c]	
low 5-FU group	62 (64.6)
high 5-FU group	34 (35.4)
Total dose of preoperative UFT (g)	3.0, 1.0–6.0[a]
Interval between most recent dose of UFT and operation	
$\leqslant 12$ h	70 (80.5)
> 12 h	17 (19.5)
unknown[b]	9
Postoperative adjuvant chemotherapy	
Regimen A[c] ('MMC')	47 (49.0)
Regimen B[c] ('MMC + UFT')	49 (51.0)

[a]Median, range.
[b]Unknown cases were excluded from statistical analysis.
[c]See Patients and methods.

Patient survival

There was a significant difference in survival between the high 5-FU group and the low 5-FU group (p=0.0465), in that the high 5-FU group had a more favorable prognosis (Fig. 2). Figure 3 shows the survival curves of the two groups of patients on Regimen A and Regimen B, i.e. classified according to

Table 2. Comparison of clinicopathological characteristics between the low and high 5-FU groups in colorectal cancer patients.

Variable	No. of carcinomas (%)		p value
	Low 5-FU group[a] (n=62)	High 5-FU group[a] (n=34)	
Age (years)	62, 41–72[b]	59, 43–74[b]	0.5075[d]
Sex			0.0610
male	43 (69.4)	17 (50.0)	
female	19 (30.6)	17 (50.0)	
Tumor location			0.7408
colon	35 (56.5)	18 (52.9)	
rectum	27 (43.6)	16 (47.1)	
Maximal tumor diameter (cm)	5.9, 2.3–10.0[b]	5.0, 2.5–9.8[b]	0.5337[d]
T			
T2	7 (11.7)	4 (12.5)	
T3	31 (51.7)	19 (59.4)	
T4	22 (36.7)	9 (28.1)	
unknown[c]	2	2	
N			0.1449
N0	37 (62.7)	15 (46.9)	
N1/N2	22 (37.3)	17 (53.1)	
unknown[c]	3	2	
M			0.5199
M0	56 (90.3)	32 (94.1)	
M1	6 (9.7)	2 (5.9)	
Histologic type			0.4961
well differentiated	25 (40.3)	15 (46.9)	
moderately differentiated	34 (54.8)	14 (43.8)	
poorly differentiated/ Mucinous	3 (4.8)	3 (9.4)	
unknown[c]	0	1	
Lymphatic invasion			0.5073
absent	17 (27.4)	7 (21.2)	
present	45 (72.6)	26 (78.8)	
unknown[c]	0	1	
Venous invasion			0.7416
absent	36 (58.1)	18 (54.5)	
present	26 (41.9)	15 (45.5)	
unknown[c]	0	1	
Stage			0.6401
I	6 (10.0)	3 (9.4)	
II	27 (45.0)	11 (34.4)	
III	20 (33.3)	15 (46.9)	
IV	7 (11.7)	3 (9.4)	
unknown[c]	2	2	
Total dose of preoperative UFT (g)	3.00, 1.0–6.0[b]	3.00, 1.0–6.0[b]	0.1615[d]
Interval between most recent dose of UFT and operation			0.8434
$\leqslant$12 h	43 (81.1)	27 (79.4)	
$>$12 h	10 (18.9)	7 (20.6)	
unknown[c]	9	0	

[a]See Patients and methods.
[b]Median, range.
[c]Unknown cases were excluded from statistical analysis.
[d]Mann–Whitney's U-test.

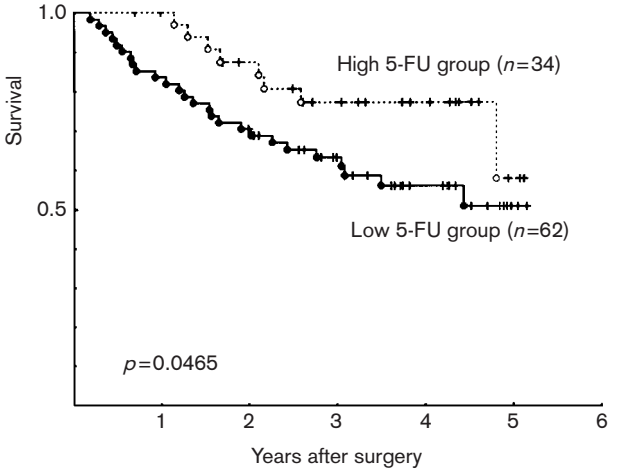

Figure 2. Survival curves for two groups of patients from the low 5-FU group (●) and the high 5-FU group (○). Membership of the high 5-FU group indicated a fair prognosis compared with the low 5-FU group, the difference was significant (p=0.0465).

whether they belonged to the low or high 5-FU group. There were no differences between Regimen A and Regimen B in either group.

Prognostic value of low 5-FU and high 5-FU values

The Cox proportional-hazards regression model was used to assess the effects of different variables on patient survival. As shown in Table 3, five factors (stage, histologic type, 5-FU status in tumor tissue, total dose of preoperative UFT and treatment group) were included. Two independent variables, i.e. stage and 5-FU status in tumor tissue, were found to be significant for the prediction of survival (Table 4). The total dose of preoperative UFT and treatment group were not significant prognostic variables.

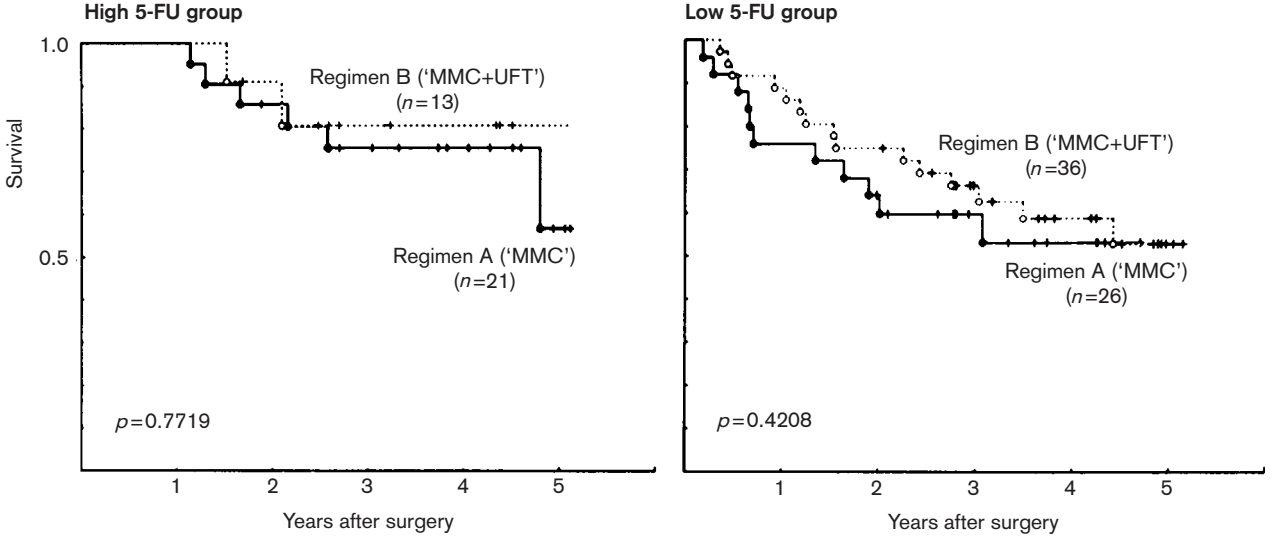

Figure 3. Survival curves for two groups of patients under Regimen A (●) and Regimen B (○) according to their membership of the low 5-FU group or the high 5-FU group. There was no difference between Regimen A and Regimen B in either group.

Table 3. Variables used in multivariate analyses.

Variable	Classes
Stage	I; II; III; IV
Histologic type	well differentiated; moderately differentiated; poorly differentiated/mucinous
5-FU status in tumor tissue	low 5-FU group; high 5-FU group
Total dose of preoperative UFT administration	g
Treatment group	Regimen A ('MMC'); Regimen B ('MMC + UFT')

Table 4. Results of multivariate analysis using Cox's proportional-hazards regression model

Variable	Regression coefficient	SE	Risk ratio	95% CI	*p* value
Stage	0.2314	0.0560	1.2604	1.1293–1.4066	<0.0001
5-FU status in tumor tissue[a]	0.9702	0.4067	2.6385	1.1889–5.8552	0.0170

[a]Low 5-FU group and high 5-FU group.

Discussion

Some previous clinical trials of preoperative treatment with the 5-FU analog (UFT or tegafur) in colorectal and gastric cancer patients in Japan failed to show any impact on patient survival.[9,10,11,13] However, Nio *et al.*[12] reported a clinical response in primary gastric cancer patients as assessed by endoscopy or upper gastrointestinal series, and a histological effect, such as necrosis or disappearance of the tumor, or replacement of the tumor by fibrosis after preoperative UFT administration (300–600 mg/day for 7–36 days). Fujii *et al.*[14,15] also reported a histopathological effect, including necrosis or disappearance of tumor cells induced by preoperative UFT administration (600 mg/day for 10 days) in colorectal cancer patients. This is at variance with the findings in the current study, which showed no histological effects of preoperative UFT. Differences in the total dose of preoperative UFT given per patient may be responsible for the observed result, i.e. the total dose of preoperative UFT per patient in the current study (median 3.0 g; range 1.0–6.0 g) was considerably lower than in Nio *et al.*'s study[12] (range 2.4–21.6 g) or Fujii *et al.*'s study[15] [7.76±3.27 g (mean±SD)].

High uptake of 5-FU by tumor tissue after administration of 5-FU or 5-FU analogs is essential for an antitumor effect. The current study revealed that colorectal cancer patients with higher uptake of 5-FU by tumor tissue following preoperative UFT administration had a favorable prognosis compared to those with lower 5-FU uptake and that 5-FU status (high or low 5-FU uptake) in tumor tissue, as well as stage, is an independent prognostic variable for patient survival according to Cox's regression analysis. There have been no reports evaluating the correlation between 5-FU uptake by primary tumor tissue following preoperative 5-FU analog administration and prognosis in patients with gastrointestinal tract cancer, except one trial.[9] Arima *et al.*[9] reported giving tegafur (1500 mg/day for 3 days) preoperatively to 23 patients with advanced gastric cancer and measuring 5-FU uptake by the primary tumor tissue obtained intraoperatively. The results showed no statistically significant correlation between the 5-FU uptake by the primary tumor tissue and patient outcome. This is at variance with the findings in the current study, which indicated a favorable prognosis in patients with increased 5-FU uptake in tumor tissue. The small number of patients in Arima *et al.*'s study[9] may be responsible for this discrepancy. In fact, in Arima *et al.*'s study,[9] the high primary tumor tissue 5-FU uptake (n=12) group actually did have a more favorable outcome than the low 5-FU uptake group (n=11), but the difference failed to achieve significance (p=0.184 by Wilcoxon's test).

We speculate that the antitumor effect induced by preoperative UFT administration may be at least partly responsible for the favorable prognosis in patients with increased 5-FU uptake by tumor tissue revealed in the current study. It was not any histopathologic effects (necrosis or disappearance of tumor cells), but possibly subclinical effects, such as inhibition of angiogenesis, etc., that may have been induced by preoperative UFT in the current study. Yonekura *et al.*[27] reported that UFT has a stronger angiogenesis-inhibitory effect, partly due to its pharmacokinetic properties characterized by maintaining higher and more sustained blood levels of 5-FU, and partly due to the inhibitory effects of the UFT-specific metabolites, γ-hydroxybutyric acid and γ-butyro-lactone. Nishimura *et al.*[13] reported a reduction in proliferating cell nuclear antigen labeling index in primary colorectal tumor tissue as a result of preoperative UFT administration (400 mg/day for 10 days or more), which may indicate inhibition of DNA synthesis in tumor cell cycle kinetics.

Arima *et al.*[9] reported that when 5-FU uptake by lymph node tissue obtained from patients intraoperatively was measured in advanced gastric cancer patients given tegafur (1500 mg/day for 3 days) preoperatively, the 5-year survival rate was significantly better in the high 5-FU uptake group than in the low 5-FU uptake group. Kuroda *et al.*[10] also reported a correlation between 5-FU uptake by lymph node tissue following preoperative tegafur administration (500–1000 mg/day for 7 days) to colorectal cancer patients and tumor recurrence. From the observations in these reports and the results of our own study, we conclude that high 5-FU uptake by tumor and/or

lymph node tissue induced by preoperative UFT administration is associated with improved patient outcome. Accordingly, assessment of tumor tissue 5-FU uptake following preoperative UFT administration may provide information that will allow prediction of fluoropyrimidine sensitivity and selection of the patient group to receive postoperative UFT chemotherapy. The present study failed to demonstrate any significant difference in survival between high 5-FU patients given Regimen A ('MMC') and Regimen B ('MMC+UFT'). Because the high-5-FU group formed a subset of patients and they had not been randomly assigned to Regimen A or Regimen B, a prospective randomized control trial in a large number of patients is needed to clarify this issue.

In the current study, no clinicopathological variables were found to be independently related to the low colorectal tumor tissue 5-FU group versus high 5-FU group. We suspect that other factors, such as dihydropyrimidine dehydrogenase (DPD) activity, may be related to high 5-FU uptake by tumor tissue following preoperative UFT administration. More than 80% of the 5-FU dose administered is degraded within 24 h after a bolus injection in a three-step pathway that is initially catalyzed by the rate-limiting enzyme DPD and this may be one of the factors limiting the efficacy of 5-FU in solid tumors.[28] Etienne *et al.*[29] reported that 5-FU catabolism in target cells is a determinant factor for 5-FU responsiveness in cancer patients and justifies the clinical use of specific DPD inhibitors as 5-FU biomodulators. We also suspect that tumor vascularity may be partly responsible for 5-FU uptake by tumor tissue after preoperative UFT administration. Shimoyama *et al.*[30] reported that the morphologic changes of tumor vessels induced by tumor progression and the vascular patterns of colorectal tumors are associated with 5-FU uptake by tumor tissue following preoperative UFT administration. The role of 5-FU and its metabolites in angiogenesis/vascularity in solid tumors remains unclear. Further study is needed.

Conclusion

In conclusion, the current study revealed that the increased uptake of 5-FU by tumor tissue following preoperative oral administration of UFT is an independent prognostic factor in colorectal cancer patients. This variable needs to be considered in the design of future therapeutic trials.

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