Uracil-Tegafur as an Adjuvant for Hepatocellular Carcinoma: A Randomized Trial

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Frequent recurrence of hepatocellular carcinoma (HCC) after surgery remains a major clinical problem. This randomized controlled trial evaluated whether postoperative adjuvant therapy with oral uracil-tegafur (UFT) prevents recurrence of HCC. A total of 160 patients who underwent curative hepatic resection for HCC were randomly assigned to receive either 300 mg/day of UFT for 1 year after surgery (n = 79, UFT group) or surgery alone (n = 80, control group). The primary endpoint was recurrence-free survival, and the secondary endpoint was overall survival. Other study variables included liver function and type of recurrence. During a median follow-up of 4.8 years (range: 0.5-7.9), recurrence-free survival curves in the groups were similar (_P_ = .87). Overall survival was slightly but not significantly worse in the UFT group than in the control group (_P_ = .08). The rates of recurrence-free and overall survival at 5 years were 29% and 58%, respectively, in the UFT group, as compared with 29% and 73%, respectively, in the control group. The hazard ratio for recurrence in the UFT group, relative to the control, was 1.01 (95% confidence interval: 0.84-1.22, _P_ = .87). The proportion of patients with advanced recurrence (i.e., multiple, extrahepatic, or associated with vascular invasion) was significantly higher in the UFT group (74%, 43 of 58 patients with recurrence) than in the control group (53%, 30 of 57) (_P_ = .02). In conclusion, our results offer no evidence to support potential benefits of adjuvant chemotherapy with UFT after surgery in patients with HCC and suggest that such treatment may even worsen overall survival. (HEPATOLOGY 2006;44:891-895.)

Hepatic resection has been established as one of the most effective and safe therapeutic options for hepatocellular carcinoma (HCC).[1,2] However, frequent recurrence of HCC even after curative surgery remains a major clinical problem.[3] Several adjuvant treatments have been used to prevent recurrence after surgery, but their effectiveness remains controversial.[4-7] Uracil-tegafur (UFT, Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) combines tegafur, a prodrug of 5-fluorouracil, with uracil, a biochemical modulator, in a molar ratio of 4:1. UFT has been reported to be effective against colorectal[8] and lung adenocarcinomas,[9] as well as HCC.[10,11] We tested the hypothesis that adjuvant chemotherapy with UFT can prevent disease recurrence after hepatic resection in patients with HCC. Because UFT is administered orally, we considered that this treatment would be clinically useful if its effectiveness could be confirmed.

Patients and Methods

Eligibility Criteria. Patients with HCC who had undergone their first curative hepatic resection at Tokyo University Hospital were eligible for this trial if they met the following entry criteria: cirrhosis of Child-Pugh class A or B; adequate bone marrow and renal functions (white blood cell count $>4.0 \times 10^3/\mu L$, platelet count $>50 \times 10^3/\mu L$, and serum creatinine level <1.5 mg/dL); and an age between 15 and 79 years. The exclusion criteria were the presence of clinically confirmed extrahepatic metastasis, macroscopic evidence of tumor thrombus in the infe-

rior vena cava or the main portal vein, other previous or synchronous malignant disorders, and postoperative dysfunction of any organ.

Study Design. The protocol for this trial was approved by the local ethical committee. The English summary of the protocol has been disclosed (registration number: C000000445) in the Clinical Trials Registry managed by the University Hospital Medical Information Network in Japan, which can be accessed free on the internet (www.umin.ac.jp/ctr/index.htm).The protocol was explained to eligible patients, and informed consent was obtained from all subjects before enrollment. Enrolled patients were stratified according to age (15-59 years vs. 60-79 years), the indocyanine green retention rate at 15 minutes (<20% vs. ≥20%), and the presence or absence of macroscopically evident vascular invasion. Patients were randomly assigned to either the UFT group or the control group by the minimization technique.[12] We created the minimization program using Microsoft Excel (for Windows) and Visual Basic. A single investigator (K.H.) not involved in surgery or patient follow-up was responsible for patient allocation and enrollment, group assignment, and informing other investigators of the assigned treatment. Because a placebo was unavailable, the study was not blinded.

The UFT group received oral UFT (300 mg/day) for 1 year after surgery. The lower limit of the recommended dose was used to avoid drug-induced liver dysfunction, taking into account the severely compromised liver function of the patients at study entry. The control group received surgery alone. During the trial period, no patient received other anticancer drugs or any antiviral therapy to treat hepatitis. After surgery, patients in both groups underwent ultrasonography and measurement of tumor markers (α-fetoprotein and des-γ-carboxy prothrombin) every 2 months, dynamic computed tomography every 4 months, and chest radiography every 6 months, as had been done in a previous study.[6] If intrahepatic recurrence was suspected, hepatic angiography followed by Lipiodol computed tomography was performed. Recurrence was defined as lesions with typical findings of HCC on two or more imaging methods. In patients who had recurrence or the development of another malignant disorder, treatment with UFT was withdrawn. Patients with local recurrence in the liver underwent a second hepatic resection, if the functional reserve of the liver permitted operation and curative surgery was possible. Other patients received local ablation, systematic chemotherapy, or transcatheter hepatic arterial chemoembolization, if possible.

The primary endpoint was recurrence-free survival, and the secondary endpoint was overall survival. Other study variables included recurrence type and liver func-
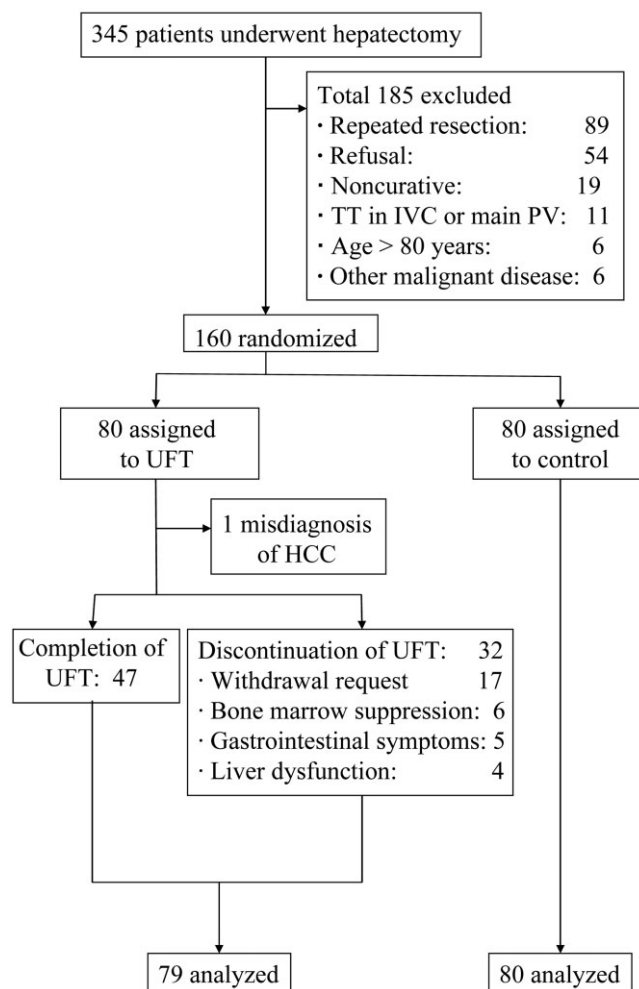

Fig. 1. The trial profile. TT, tumor thrombus; IVC, inferior vena cava; PV, portal vein; UFT, uracil-tegafur; HCC, hepatocellular carcinoma.

tion (serum albumin, alanine aminotransferase [ALT], and total bilirubin levels), evaluated 1 year after surgery or before further treatment in patients who had recurrence within 1 year.

Statistical Analysis. All analyses were performed on an intention-to-treat basis. The Wilcoxon rank-sum test and Fisher's exact test were used for comparisons of continuous and the categorical data, respectively. All continuous data are expressed as medians with ranges. Recurrence-free and overall survival curves were estimated by the Kaplan-Meier method, and survival rates were compared between the groups by the log-rank test. The effect of treatment with UFT on recurrence-free survival was estimated using a Cox's proportional-hazards model with no other covariate. The results of this analysis are expressed as hazard ratios with 95% confidence intervals. Statistical significance was defined as a P value less than .05.

We hypothesized that treatment with UFT would increase the rate of recurrence-free survival at 3 years from

Table 1. Baseline Characteristics

Variables	UFT (n = 79)	Control (n = 80)	P
Age (yr)*	65 (29-75)	64 (35-78)	.93
Gender (male/female)	60/19	65/15	.41
Child-Pugh class (A/B)	68/11	70/10	.82
ICG R15 (%)*,**	15 (2-44)	15 (5-40)	.40
Hepatitis (HBV/HCV/none)	14/58/7	15/56/9	–
Background liver (cirrhosis/noncirrhosis)	42/37	38/42	.53
Serum albumin before surgery (g/dL)*	3.5 (2.3-4.5)	3.7 (2.7-4.4)	.11
Serum ALT before surgery (IU/L)*	51 (9-291)	47 (8-174)	.45
Serum total bilirubin before surgery (mg/dL)*	0.8 (0.4-1.5)	0.8 (0.3-1.8)	.95
Tumor number (single/multiple)	53/26	58/22	.50
Tumor size (mm)*	33 (12-120)	34 (7-130)	.65
Vascular invasion (yes/no)	18/61	17/63	.85
Alpha-fetoprotein (ng/mL)*	29 (2-49715)	29 (1-49388)	.47
Hepatectomy procedure (major/minor)	16/63	20/60	.57
Blood loss (mL)*	480 (15-2957)	615 (70-4830)	.39
Hospital stay (days)*	17 (9-48)	18 (9-41)	.41
Mortality	0 (0%)	0 (0%)	–

*Median with range.

**ICG R15, indocyanine green retention rate at 15 min.

30%[6] to 50%, and that 146 patients would be required to detect a significant difference with a 1-tailed type I error of 5% and a statistical power of 80%. Assuming a 10% dropout rate, we set a goal of 160 patients for this trial. Interim analysis was not scheduled. Calculations were performed with JMP 5.1 computer software (SAS Institute Inc., Cary, NC).

Role of Funding Sources. The sponsors of this study had no role in study design; in the collection, analysis, or interpretation of the data; in writing the report; or in the decision to submit the paper for publication.

Results

From 1997 through 2002, 345 patients underwent a first curative liver resection for HCC at Tokyo University Hospital. A total of 185 patients were excluded for the reasons shown in Fig. 1. The remaining 160 patients were randomly assigned to either the UFT group (n = 80) or the control (n = 80) group. One patient assigned to the UFT group was found to be ineligible after enrollment because HCC had been misdiagnosed. Data from the other 159 patients were analyzed. The baseline characteristics of the two groups were similar (Table 1). Treatment with UFT was temporarily or permanently discontinued in 32 patients (41%) because of bone marrow suppression (n = 6), withdrawal of consent (n = 17), nausea (n = 3), diarrhea (n = 2), and liver dysfunction (n = 4). All adverse events responded to conservative therapy.

Median follow-up was 4.8 years (range: 0.5-7.9). Only one patient in the UFT group was lost to follow up. Recurrence-free survival ($P = .87$) and overall survival ($P = .08$) were similar in the groups (Fig. 2). The rates of recurrence-free survival at 3 and 5 years were respectively 41% and 29% in the UFT group, as compared with 37% and 29% in the control group. The rates of overall survival at 3 and 5 years were respectively 90%, and 58% in the UFT group, as compared with 92% and 73% in the

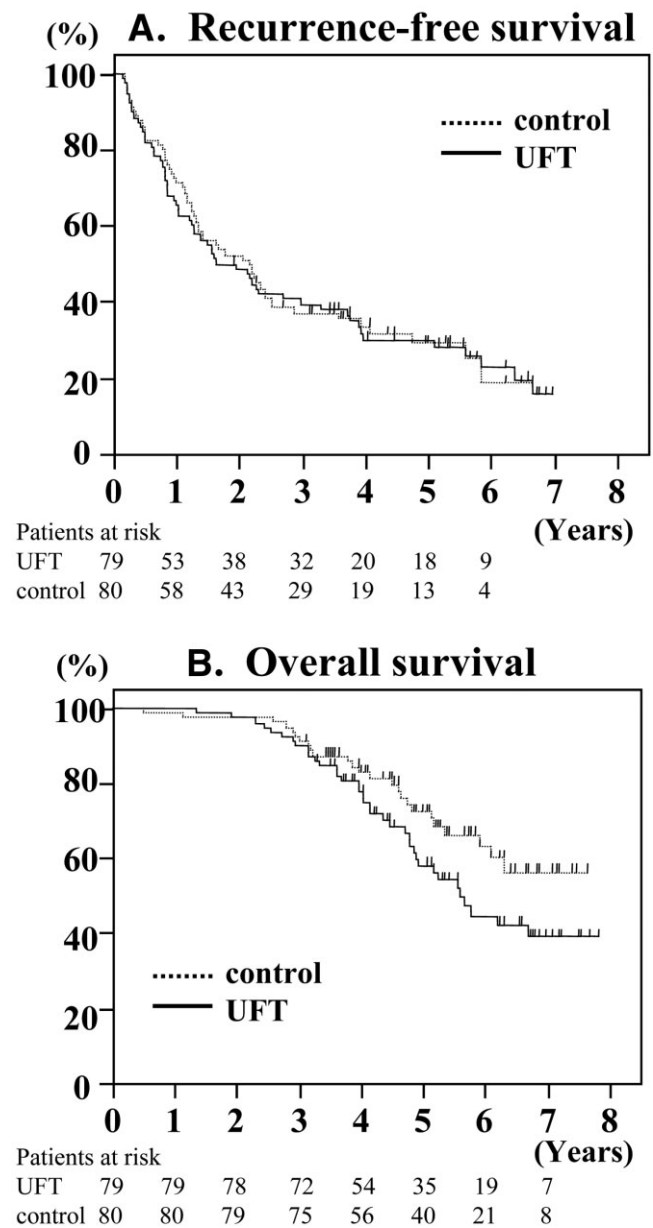Fig. 2. (A) Recurrence-free survival curves of the UFT (line) and the control (dotted line) groups. Five-year recurrence-free rates were similar (29% vs. 29%, $P = .87$) between the two groups. (B) Overall survival curves of the 2 groups. Five-year overall survival rate of the UFT group was slightly lower than that of the control group (58% vs. 73%, $P = .08$), although the difference was not statistically significant.

control group. The hazard ratio for recurrence in the UFT group, relative to the control, was 1.01 (95% confidence interval: 0.84-1.22, $P = .87$).

Recurrence was advanced (*i.e.*, multiple, extrahepatic, or associated with vascular invasion) in 43 of the 58 patients (74%) with recurrence in the UFT group, as compared with 30 of the 57 (53%) patients with recurrence in the control group (Table 2). The proportion of patients with advanced recurrence was significantly higher in the UFT group than in the control group ($P = .02$). Liver function after surgery, assessed on the basis of serum albumin, alanine aminotransferase, and total bilirubin levels, did not differ significantly between the groups (Table 3).

Discussion

In this study, recurrence-free survival curves were nearly identical in the UFT group and control group. This trial provided no evidence that treatment with oral UFT prevented postoperative recurrence of HCC after hepatic resection, as compared with surgery alone.

Theoretically, HCC recurs through metastasis from a primary tumor or the development of a second primary tumor in an injured liver.[3] Transcatheter arterial chemoembolization with ^{131}I-labeled iodized oil[5] and adoptive immunotherapy[6] have been reported to be effective for the prevention of metastasis. However, these adjuvant therapies are extremely expensive and require special equipment and techniques to prepare and dispose of the isotope labeling material[5] or to purify and culture the patient-related lymphocytes.[6] Retinoids[4] and interferon[7] have also been used as adjuvant therapy to prevent the development of second primary tumors, but the value of these treatments is not widely accepted, in spite of the recent promising result.[13] Adjuvant therapy that can prevent the recurrence of HCC after curative resection thus remains to be established. Because UFT has been reported to be effective against HCC,[10,11] we expected that it

Table 2. Postoperative Recurrence

Variables	UFT (n = 79)	Control (n = 80)	P
Recurrence			.86
No	21	23	
Yes	58	57	
Recurrence type			.02
Advanced*	43 (74%)	30 (53%)	
Less advanced†	15 (26%)	27 (47%)	
Treatment for primary recurrence			.08
Surgical	16 (28%)	25 (44%)	
Nonsurgical	42 (72%)	32 (56%)	

*Multiple, extrahepatic, or vascular invasion-associated recurrence.
†Solitary and intrahepatic recurrence without vascular invasion.

Table 3. Postoperative Liver Function

Variables	UFT (n = 79)	Control (n = 80)	P
Serum albumin after surgery (g/dL)	3.8 (2.5-4.6)	3.8 (3.1-4.6)	.06
Serum ALT after surgery (IU/L)	40 (14-144)	49 (11-298)	.45
Serum total bilirubin after surgery (mg/dL)	0.8 (0.4-2.3)	0.7 (0.3-2.1)	.05

NOTE. Data are shown as median with range. Data were obtained 1 year after surgery or before treatment for recurrence.

would prevent metastatic recurrence caused by HCC cells present in the microcirculation. However, the results of our study were negative.

Contrary to expectations, overall survival appeared to be worse in the UFT group than in the control group, despite identical recurrence-free survival curves. These seemingly paradoxical results might be attributed to the difference between the groups in the pattern of recurrence, *i.e.*, advanced recurrence associated with vascular invasion, multiple tumors, and extrahepatic disease was more frequent in the UFT group. In fact, second resections, established as the most effective treatment for recurrent HCC,[14] were feasible in only 28% of the 58 patients with primary recurrence in the UFT group, as compared with 44% of the 57 patients with primary recurrence in the control group ($P = .08$, Table 2). These results suggest that UFT might have some potentially undesirable effects on HCC.

A previous study suggested that accelerated repopulation of surviving tumor cells can occur after sequential chemotherapy with 5-fluorouracil.[15] Although the causal relation between UFT and recurrence pattern is beyond the scope of our study, UFT may have promoted repopulation of HCC cells surviving in the microcirculation after surgery, thereby leading to the marginally higher incidence of advanced recurrence in the UFT group. Lai et al. reported that extrahepatic recurrence of HCC might be related to adjuvant chemotherapy with epirubicin.[16] However, further studies are needed to confirm these findings.

One reason for the poorer overall survival in the UFT group might be adverse effects of UFT on liver function. A previous study suggested that adjuvant chemotherapy (4′-epi-doxorubicin alone or in combination of UFT) after surgery for HCC might worsen overall survival in patients with cirrhosis by negatively affecting liver function.[17] In our study, however, the results of conventional liver function tests did not differ between the groups (Table 3), suggesting that adverse effects of UFT on liver function were negligible. To evaluate the clinical significance of UFT taking its possible effects on liver function into consideration, overall survival would be more suit-

able as the primary endpoint, because the patients have underlying liver disease and, unlike most cancers, a significant proportion of deaths in HCC patients are due to liver disease rather than to HCC.

Recently, UFT has received considerable attention as an effective anticancer drug.[8-11] The results of our clinical trial suggest that the effectiveness of UFT may have been overestimated in previous studies, perhaps because of publication bias. In patients undergoing surgery for HCC, however, our results offer no evidence to support potential benefits of adjuvant chemotherapy with UFT.

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