A Randomized Phase II Trial of Adjuvant Chemotherapy With Uracil/Tegafur and Gemcitabine Versus Gemcitabine Alone in Patients With Resected Pancreatic Cancer

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BACKGROUND. There have been few randomized studies of adjuvant chemotherapy using gemcitabine (GEM) in patients with resected pancreatic cancer.

METHODS. Patients with invasive ductal pancreatic cancer who underwent radical surgery were enrolled and assigned to receive uracil/tegafur (UFT) and GEM together (GU) or GEM alone (G). GEM was administrated at a dosage of 1 g/m^2 intravenously weekly 3 of 4 weeks and UFT at a dosage of 200 mg/day orally continuously. Eligibility included resection status 0 or 1, and no previous chemo- or/and radiation therapy. The primary endpoint was disease-free survival (DFS), and secondary endpoints included overall survival (OS) and toxicity.

RESULTS. Between 2002 and 2005, 100 patients were randomized into the 2 arms of the trial (50 patients to GU and 50 to G). One patient in the G group was found to be ineligible. Baseline characteristics were well balanced between the 2 groups. With a median observation period of 21 months, the 1- and 3-year DFS rates were 50.0% and 17.7% in the GU group and 49.0% and 21.6% in the G group, respectively. The median OS was 21.2 months in the GU group and 29.8 months in the G group. Toxicity was minor and acceptable, less than grade 4 in both groups.

CONCLUSIONS. Postoperative GEM-based adjuvant chemotherapy was safe and well tolerated. However, addition of UFT with GEM did not improve DFS as compared with GEM alone. Further clinical trial resources for adjuvant chemotherapy should address other combinations and novel agents. ***Cancer*** **2008;113:2448–56.**

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Pancreatic cancer is 1 of the most lethal human malignancies and continues to be a major unsolved health problem. It is the fourth leading cause of death from cancer in the United States[1] and the fifth in Japan.[2] Despite the recent advances in the management of the disease, long-term survival remains poor, with a 5-year survival rate of about 5%.[1,2]

Surgery is the only means to obtain a cure for patients with pancreatic cancer. Even with advanced cancer, the best survival rates are achieved after surgical resection.[3,4] However, because of the high incidence of recurrences, the 5-year survival rate of patients who undergo resection remains low, approximately 20%.[3,5] Extended resections do not improve survival, as demonstrated in several randomized trials.[6-8] These facts indicate that, to achieve long-term disease control in patients with pancreatic cancer, it is important to develop an effective multidisciplinary therapy, a combination of surgery with other nonsurgical therapies such as radiation and chemotherapy.

In fact, it has been clearly shown that adjuvant chemotherapy prolongs postoperative survival in several types of malignancies, including breast,[9] colorectal,[10] and gastric cancer.[11] To date, several randomized studies of adjuvant therapy have been conducted in patients with resected pancreatic cancer. The Gastrointestinal Tumor Study Group (GITSG) first reported, in a multicenter randomized-controlled study, that adjuvant chemoradiation therapy prolonged the postoperative survival of patients with resected pancreatic cancer.[12] However, the results of several subsequent trials, in which 5-fluorouracil (5-FU)-based chemotherapy was applied, were inconsistent.[13-17] Although Stocken et al showed by meta-analysis that 5-FU-based chemotherapy is an effective adjuvant treatment in pancreatic cancer, the survival rate of patients with adjuvant chemotherapy was still poor, with a median survival time of only 19.0 months.[18]

Since Burris et al first reported an improvement in survival and clinical benefits with gemcitabine, an analog of deoxycytidine, compared with 5-FU for advanced pancreatic cancer,[19] gemcitabine has become a major first-line reagent for patients with unresectable pancreatic cancer. The same year, when they published their paper showing the benefits of gemcitabine therapy, the German group started a randomized controlled trial (CONKO-001) to estimate the benefits of adjuvant chemotherapy with gemcitabine for patients with resected pancreatic cancer, and recently reported that it significantly delayed the development of recurrent diseases.[20] However, there exist only a few other trials of adjuvant chemotherapy with gemcitabine for patients with resected pancreatic cancer.

With this background, we planned a similarly randomized trial to evaluate the survival benefit of gemcitabine adjuvant therapy in combination with another reagent. For this purpose, we used tegafur/uracil (UFT). UFT is an oral fluoropyrimidine agent composed of tegafur and uracil at 1:4 fixed molar ratio to increase the tumor concentration and antineoplastic activity of 5-FU.[21] In vitro experiments showed that pretreatment with 5-FU increased the cell intensity and toxicity of gemcitabine by synergistic activity.[22] Furthermore, the combination of gemcitabine and UFT has already shown a high tumor response rate in patients with lung cancer.[23,24] It has also been shown that a combination of capecitabine, another prodrug of 5-FU, and gemcitabine increased the survival rate of patients with unresectable pancreatic cancer with good performance status compared with those produced by gemcitabine treatment alone.[25]

In 2002, we initiated a multicenter randomized controlled phase II trial to estimate the possible efficacy of a UFT combination with gemcitabine, compared with gemcitabine alone, for adjuvant chemotherapy in patients with resected pancreatic cancer.

MATERIALS AND METHODS

Patients and Design

Patient recruitment for the multicenter randomized phase II trial was begun in May 2002 and was closed in December 2005 in 19 Japanese institutions. Patients who had pancreatic cancer histologically verified as invasive ductal carcinoma and who had undergone macroscopic complete resection were enrolled. Patients with carcinoma in situ were excluded. Patients with prior radiation or neoadjuvant chemotherapy or with distant metastasis except minimal para-aortic lymph node metastasis were excluded from this study. Other eligibility criteria included: being aged 20 years or older and 79 years or younger at the time of registration; absence of active infection, significant cardiac disease, brain disease, and/or active malignancies other than pancreatic cancer; and adequate hematologic, renal, and hepatologic function (leukocytes $\geq$4000/mm^3, hemoglobin $\geq$9.0 g/dL, platelets $\geq 1 \times 10^5$/mm^3, creatinine $\leq$1.5$\times$ upper limit of normal [ULN], total bilirubin $\leq 3 \times$ ULN, transaminase $\leq 2.5 \times$ ULN). The protocol was approved by the institutional review board at each study site, and all patients provided written informed

consent. The patients were registered within 10 weeks of surgery and were then randomly assigned to 1 of 2 groups: adjuvant chemotherapy with a gemcitabine alone (GEM) group and a gemcitabine + UFT (GEM + UFT) group. All patients were diagnosed as free of recurrences by computed tomography postoperatively before enrollment. Randomization was performed at the coordinating center of the trial using a computer-generated procedure. Standard surgical procedures were used depending on the extent of tumor involvement and according to institutional policy. Handling and histological examination of the resected specimens were carried out according to the recommendations of the Japan Pancreatic Society.[26] During the study, vital signs and complete blood counts were obtained weekly. Additional 4-week assessments included serum biochemistry and adverse events. Imaging by computed tomography or ultrasound was carried out every 3 months. Diagnosis of recurrence was made based on the imaging findings. Treatment after recurrence was not defined.

Adjuvant Chemotherapy

Chemotherapy was started within 1 week of randomization. Patients in the GEM group received adjuvant chemotherapy of at least 4 cycles of gemcitabine every 4 weeks. Each chemotherapy cycle consisted of 3 weekly infusions of gemcitabine at 1000 mg/m^2 given by intravenous infusion during a 30-minute period, followed by a 1-week pause. Patients in the GEM + UFT group received UFT at 200 mg/day continuously in addition to gemcitabine with the same protocol as the GEM group. Patients who received 4 cycles of treatment were considered to have completed the therapy. Patients were allowed to continue the same therapy after 4 cycles. Toxicity was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events versions 2.0 (~2004) and 3.0 (~2004). If the patient showed grade 3 or worse hematologic adverse events, serum transaminase level >2.5-fold ULN, serum total bilirubin level >3.0 mg/dL, or other adverse clinical events of grade 2 or worse, chemotherapy was stopped until recovery from these criteria. The dose of gemcitabine was reduced to 800 mg/m^2 in the following cycles and to 600 mg/m^2 if additional adverse events occurred. In the GEM + UFT group, UFT was stopped if adverse events occurred even after a reduction of gemcitabine to 800 mg/m^2, with gemcitabine further reduced to 600 mg/m^2 in the following cycles. Chemotherapy was discontinued if adverse events within these criteria occurred regardless of whether the gemcitabine dose had been reduced to 600 mg/m^2.

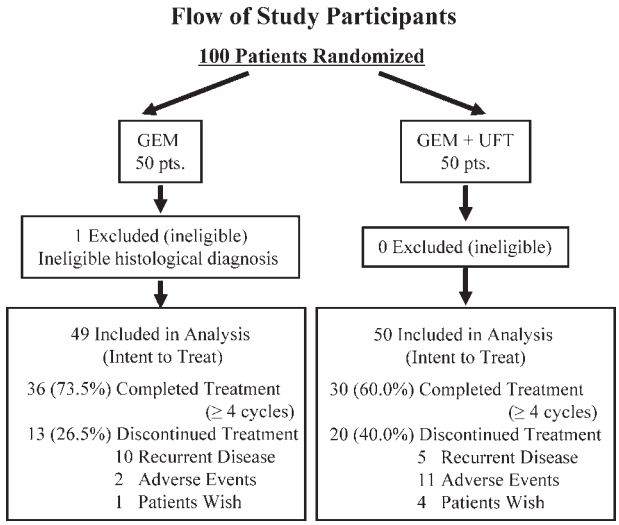

FIGURE 1. The flow of study participants is depicted. GEM indicates gemcitabine alone; UFT, tegafur/uracil.

Statistics

The primary endpoint of the study was the 1-year disease-free survival rate. Secondary endpoints included toxicity and overall survival. The duration of disease-free and overall survival was calculated from the date of surgery to the date of recurrence and death, respectively. Efficacy analyses were performed according to the intention-to-treat principle. Survival curves were drawn using the Kaplan-Meier technique, and the log-rank test was used to assess differences in survival estimates among the groups. The univariate analysis was done using the Cox proportional hazards model. Assuming a 1-year disease-free survival rate of 40% in the GEM arm, the present study was designed to enroll more than 89 patients to detect an absolute increase of at least 15% in the GEM + UFT arm, with a significance level of 5% with 90% power, and taking into consideration a dropout rate of 25%. Data analysis was performed using StatView version 5.0 (SAS Institute Inc. Cary, NC).

RESULTS

Patients

Between May 2002 and December 2005, 100 patients were recruited into the study from 19 institutions in Japan. The patients were randomized to the GEM group (n = 50) and the GEM + UFT group (n = 50) (Fig. 1). One patient in the GEM group was rated ineligible because of a histological diagnosis

TABLE 1
Characteristics of Eligible Patients

	Gemcitabine	Gemcitabine+UFT	*P*
Patients, n	49	50	
Age, median (range), y	63 (38-78)	63 (38-78)	.35
Sex, women/men	31 / 18	33 / 17	.78
Period from surgery to randomization, median (IQR), d	30.0 (26.0-37.0)	26.5 (20.25-35.75)	.41
Period from surgery to start of adjuvant chemotherapy, median (IQR), d	35.0 (27.0-41.0)	30.0 (23.25-42.50)	.48
Operative procedure, PD/DP/TP	38/8/3	38/9/3	.98
UICC stage, IA/IB/IIA/IIB/III/IV	0/1/13/26/2/7	1/1/10/33/1/4	.64
JPS stage, I/II/III/IVa/IVb	0/2/16/22/9	1/2/21/17/9	.68
Primary tumor status, 1/2/3/4	0/2/45/2	2/4/23/1	.39
Nodal status, 0/1	15/34	13/37	.61
Distant metastasis, 0/1	42/7	46/4	.32
Resection status, 0/1	32/17	41/9	.06
Histology			.88
Tubular adenocarcinoma, well/mod/poor	3/34/6	6/33/7	
Papillary adenocarcinoma	1	1	
Adenosquamous carcinoma	1	1	
Anaplastic carcinoma	1	1	
Invasive carcinoma derived from intraductal tumor	3	1	

UFT indicates tegafur/uracil; IQR, interquartile range; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; UICC, International Union Against Cancer; well, well-differentiated type, mod, moderately differentiated type; poor, poorly differentiated type. JPS, Japan Pancreas Society.

(undifferentiated carcinoma) determined after randomization. The remaining 99 patients were included in the analysis. The baseline characteristics of the patients in the 2 groups were comparable (Table 1). There was no statistical difference between the 2 groups in the median time from surgery to the start of chemotherapy of 35.0 days in the GEM group and 30.0 days in the GEM + UFT group.

Treatment Data

All patients received at least 1 dose of gemcitabine. The median number of the gemcitabine administrations for a patient was 12 times for the GEM group and 14 times for the GEM + UFT group. Median relative dose intensity within the first 4 cycles was 89.1% for the GEM group and 87.4% for the GEM + UFT group; there was no statistical difference between the 2 groups (Table 2). Median duration of UFT administration in the GEM + UFT group was 5 months, and the median relative dose intensity within the first 4 cycles was 100% (Table 2).

Thirty-six patients (73.5%) in the GEM group and 30 patients (60.0%) in the GEM + UFT group completed 4 or more cycles of treatment. The reasons for treatment discontinuation within 4 cycles in the GEM group were recurrent disease (10 patients, 76.9%), adverse events (2 patients, 15.4%), and patient's wish (1 patient, 7.7%). In the GEM + UFT group, the reasons were recurrent disease (5 patients, 25.0%), adverse events (11 patients, 55.0%), and patient's wish (4 patients, 20.0%).

TABLE 2
Total Dose and Relative Intensity

	Gemcitabine, median (range)	Gemcitabine+UFT, median (range)	*P*
Gemcitabine			
Total amount, g	19.2 (3.9-76.5)	19.2 (2.5-113.1)	.86
Administrations, n	12 (3-76)	14 (2-81)	.67
Relative dose intensity, %	89.1 (22.5-100)	87.4 (13.5-100)	.69
UFT			
Total amount, g	—	27.8 (1.2-158.0)	
Duration of administration, mo	—	5 (1-26)	
Relative dose intensity, %	—	100 (5.4-100)	

UFT indicates tegafur/uracil.

Toxicity

Although the majority of the patients, especially those in the GEM + UFT group, experienced minor toxicity, no grade 4 or higher toxicities were observed in either group (Table 3). Fifteen (30.6%) patients in the GEM group and 12 (24.0%) patients in the GEM + UFT group experienced grade 3 toxicity, mainly leukocytopenia. Two patients in the GEM group and 11 patients in the GEM + UFT group discontinued treatment within 4 cycles because of repeated toxicities despite dose modification. All toxicities were reversible and resolved with conservative treatment alone in all patients.

Efficacy

With a median observation period of 21 months (range, 3 months to 57 months), recurrent disease developed at comparable rates of 73.5% in the GEM group (36 of 49 patients) and 78% in the GEM + UFT group (39 of 50 patients). The sites of recurrence were similar in both groups (GEM group and GEM + UFT group); the local recurrence was observed in 75.0% and 69.2% of patients, respectively. The number of patients with local recurrence alone was 13 (36.1%) in the GEM group and 17 (43.6%) in the GEM + UFT group. The most frequent primary site of distant metastasis was the liver, with 12 (33.3%) patients of the GEM group and 13 (33.3%) patients of the GEM + UFT group. The estimated

TABLE 3
Summary of Toxicities

	Gemcitabine			Gemcitabine+UFT		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Total	29 (59.2%)	15 (30.6%)	0 (0.0%)	45 (90.0%)	12 (24.0%)	0 (0.0%)
Hematologic						
Leukocytes	26 (53.1%)	11 (22.4%)	0 (0.0%)	36 (72.0%)	9 (18.0%)	0 (0.0%)
Hemoglobin	20 (40.8%)	4 (8.2%)	0 (0.0%)	17 (34.0%)	2 (4.0%)	0 (0.0%)
Platelets	13 (26.5%)	3 (6.1%)	0 (0.0%)	11 (22.0%)	0 (0.0%)	0 (0.0%)
Nonhematologic						
Nausea/vomiting	10 (20.4%)	0 (0.0%)	0 (0.0%)	12 (24.0%)	0 (0.0%)	0 (0.0%)
Anorexia	9 (18.4%)	1 (2.0%)	0 (0.0%)	14 (28.0%)	1 (2.0%)	0 (0.0%)
Biochemical						
AST/ALT	11 (22.4%)	0 (0.0%)	0 (0.0%)	11 (22.0%)	1 (2.0%)	0 (0.0%)
Glucose intolerance	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.

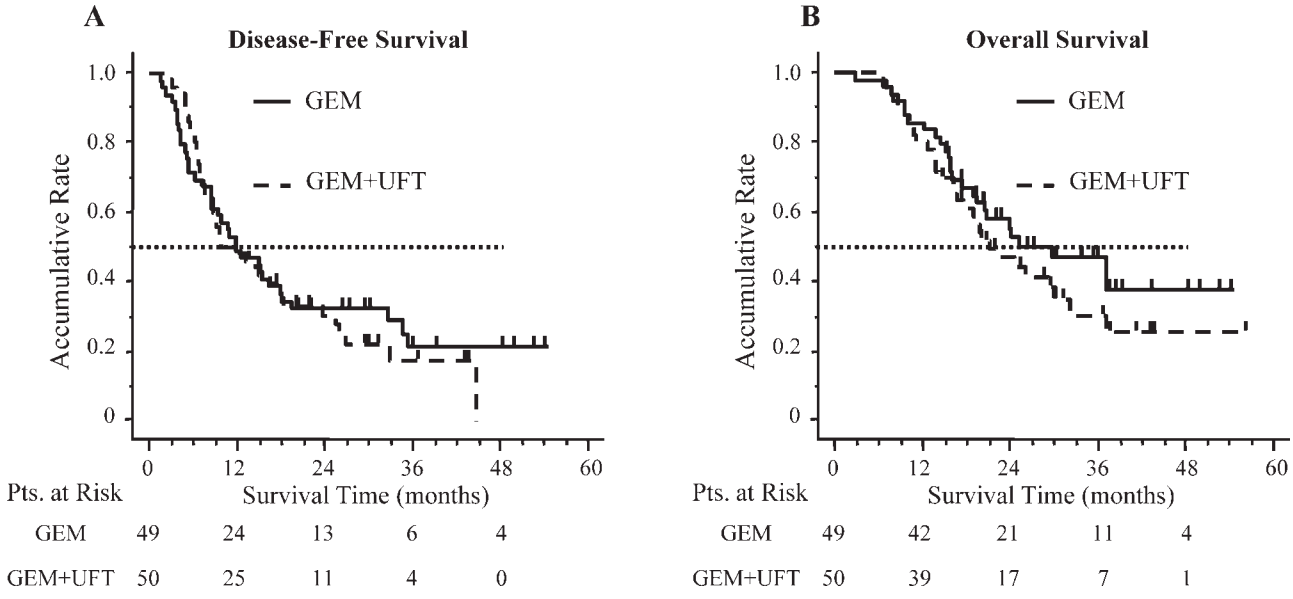

FIGURE 2. Disease-free (A) and overall (B) survival are shown. GEM indicates gemcitabine alone; Pts., patients; UFT, tegafur/uracil.

1- and 3-year disease-free survival rates were 49.0% and 21.6% in the GEM group and 50.0% and 17.7% in the GEM + UFT group, respectively. The median disease-free survival time was also comparable to 12.0 months in the GEM group and 12.3 months in the GEM + UFT group (log-rank, $P = .67$, Fig. 2A).

In the randomized patients, 57 patients (26 in the GEM group and 31 in the GEM + UFT group) died because of recurrent disease; there were no deaths attributed to any other causes in the observation period. The median overall survival time was 29.8 months in the GEM group and 21.2 months in the GEM + UFT group. The estimated survival rates at 1 and 3 years were 85.7% and 46.9% in the GEM group and 80.0% and 30.4% in the GEM + UFT group, respectively. There was no statistical difference between the overall survival times of the GEM group and the GEM + UFT group (log-rank, $P = .28$, Fig. 2B).

Prognostic Factors for Patients With Adjuvant Chemotherapy

We analyzed the clinical outcomes of all patients in this study to estimate the efficacy of adjuvant chemotherapy using gemcitabine for patients with resected pancreatic cancer. The median disease-free

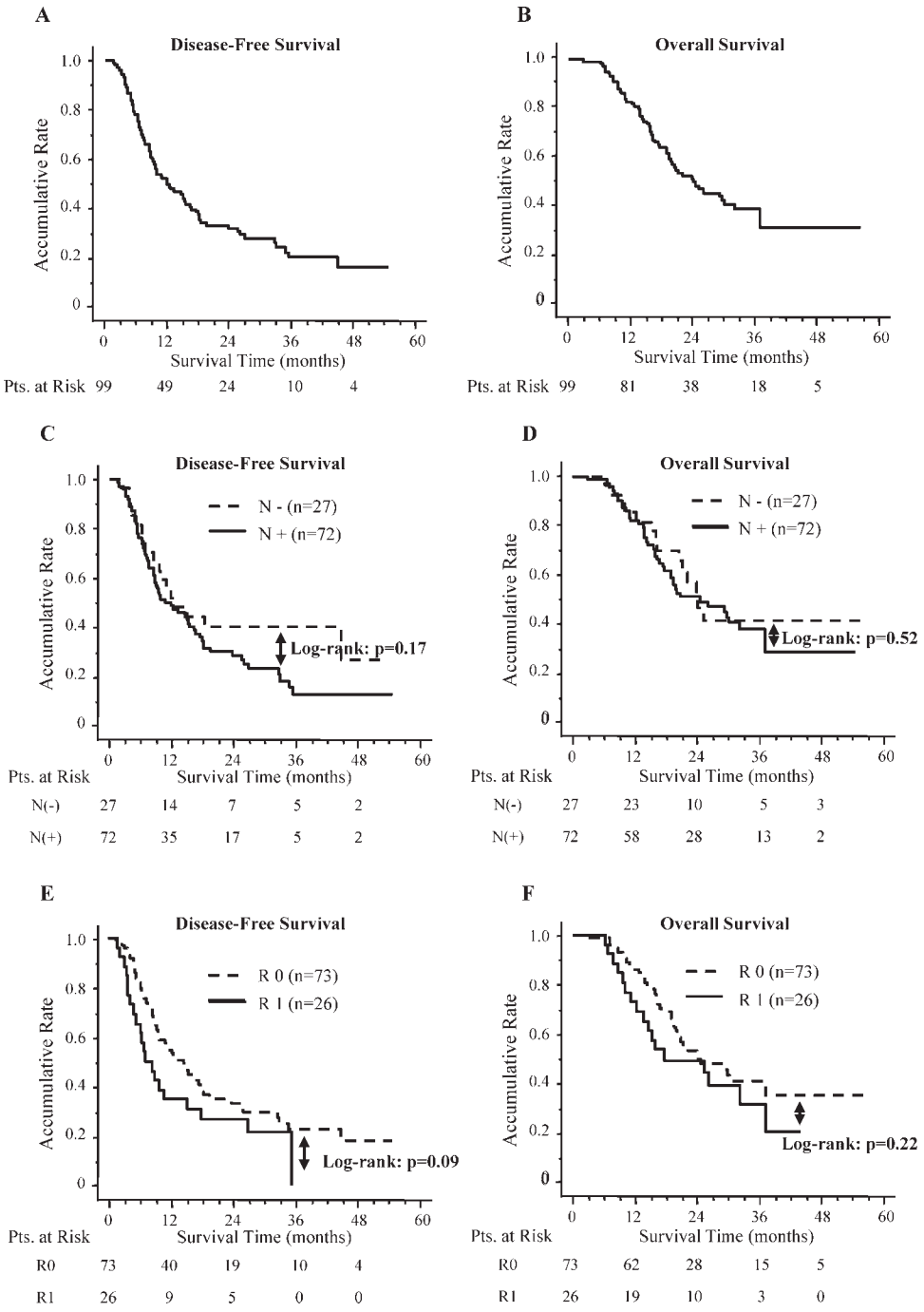

FIGURE 3. Disease-free and overall survival of all patients (Pts.) are shown: (A) disease-free survival; (B) overall survival; (C, D) disease-free (C) and overall (D) survival of the patients categorized by nodal status (solid line indicates lymph node positive [N+]; dotted line: lymph node negative [N−]); (E, F) disease-free (E) and overall (F) survival of the patients categorized by resection status (R) (solid line indicates R1; dotted line, R0).

survival time of all 99 patients in this study was 12.0 months, and the estimated 1- and 3-year disease-free survival rates were 49.5% and 19.5%, respectively (Fig. 3A). The median overall survival time of those patients was 24.1 months, and the estimated 1- and 3-year survival rates were 82.8% and 38.8%, respectively (Fig. 3B).

To assess the influence of prognostic factors, the relationships between the survival outcomes and the following variables were investigated: sex, age (≤63

years/>63 years), tumor location (head/body or tail), International Union Against Cancer stage (IA-IIA/IIB-IV), Japan Pancreas Society (JPS) stage (I-III/IVa, b), operation time (≤444 minutes/>444 minutes), blood loss during operation (≤920 mL/>920 mL), tumor size (≤2 cm/>2 cm), nodal status (negative/positive), para-aorta lymph node metastasis (negative/positive), tumor histology (poorly differentiated tubular adenocarcinoma/other), and resection status (R0/R1). We performed univariate analysis of these factors for disease-free and overall survival times. Among these factors, only the JPS stage showed a significant value for disease-free survival time (hazard ratio, 0.473; 95% confidence interval; 0.288-0.775; $P = .003$), and no factors exerted a significant influence on overall survival time.

Because factors that are known to have prognostic value for survival such as nodal status and resection status did not show significant values on univariate analysis, we performed a Kaplan-Meier analysis of the disease-free and overall survival times for all 99 patients, and categorized the outcome by these factors. As shown in univariate analysis, there were no significant differences between patients with and without lymph node metastasis with respect to disease-free and overall survival times (Fig. 3C, D). Moreover, there were no significant differences between patients with R0 and R1 resection with respect to disease-free and overall survival times (Fig. 3E, F).

DISCUSSION

For the treatment of patients with pancreatic cancer, even with advanced cancer, the best survival rates are achieved after surgical resection.[3,4] However, because of the high recurrence rate, the prognosis of the patient remains poor even after curative surgery. This indicates that it is important to establish an effective multidiscipline therapy for pancreatic cancer. In this study, we aimed to estimate the efficacy of adjuvant chemotherapy using gemcitabine and UFT for patients with resected pancreatic cancer.

Burris et al first reported in 1997 that gemcitabine improved the survival of patients with advanced pancreatic cancer, with a median survival time of 5.65 months compared with 4.41 months for patients treated with 5-FU.[19] Since then, gemcitabine has become the first-line chemotherapy for patients with pancreatic cancer. Meanwhile, several randomized studies have shown that 5-FU-based adjuvant chemotherapy can improve the survival of patients with resected pancreatic cancer.[13,27] Therefore, we strongly expected that adjuvant chemotherapy using gemcitabine would improve the survival of our patients. We thus attempted in our phase II study to optimize the efficacy of adjuvant chemotherapy by combination with gemcitabine and other agents.

We selected UFT as the agent to use in combination with gemcitabine. There were several reasons. First, in vitro analysis showed that pretreatment of pancreatic cancer cells with 5-FU increased the intracellular concentration of gemcitabine, suggesting that UFT, a prodrug of 5-FU, might have the potential to supplement the therapeutic benefits of gemcitabine.[22] Second, UFT, an oral fluoropyrimidine, might be more convenient to administer than continuous 5-FU infusion, especially in an adjuvant setting. In addition, several groups had shown favorable results from the use of a combination of gemcitabine and UFT as a treatment for advanced pancreatic cancer.[28,29]

Our study showed that adjuvant chemotherapy with gemcitabine, with or without UFT, could be carried out with acceptable safety. No grade 4 toxicities were observed in any patients in either group, and no patient died because of toxic events related to adjuvant therapy. Grade 3 hematologic toxicities were observed in about 30% of the patients in both groups. Leukocytopenia was most frequently observed, as shown in the CONKO-001 study.[20] Although a high incidence of leukocytopenia from gemcitabine has also been reported in the treatment of nonresected pancreatic cancer with 9.7% grade 3 leukocytopenia,[19] the frequency in this study was relatively high. Onoue et al have reported as well that severe leukocytopenia induced by gemcitabine administration developed readily in patients who had undergone surgical resection.[30] This suggests that it is very important to observe patients closely, especially in adjuvant chemotherapy, to avoid fatal toxicities. Nevertheless, as no serious adverse events were observed in this study, we concluded that the adjuvant chemotherapy using gemcitabine with or without UFT can be carried out safely.

Unfortunately, this study failed to show any additional benefit in using UFT in concert with gemcitabine for patients with resected pancreatic cancer. Disease-free survival was similar in both groups, with a 1-year disease-free survival rate of 49.0% in the GEM group and a 50.0% rate in the GEM + UFT group. Moreover, the overall survival rate was slightly worse among the patients of the GEM + UFT group than among those of the GEM group, with median survival time of 21.2 months and 29.8 months, respectively. Although the observation period was short, we concluded from our data that other combinations with gemcitabine must be considered as

future trials for adjuvant chemotherapy for resected pancreatic cancer.

Although UFT did not induce any survival benefits, the patients of both groups who received gemcitabine adjuvant chemotherapy after surgery experienced relatively longer survival times. The median disease-free survival time of the total of 99 patients in this study was 12.0 months, and the median overall survival time was 24.1 months. The overall median survival time is usually reported as about 10 months to 20 months for patients with resected pancreatic cancer who did not received adjuvant chemotherapy.[12-17,20] In addition, survival in this study was favorable compared with studies of adjuvant therapy for pancreatic cancer. The median overall survival time of patients with adjuvant therapy was reported as 20.0 months in the GITSG study[12] and 20.1 months in the ESPAC-1 study.[17] Also, as expected, our data were almost equivalent with the CONKO-001 study, in which the median survival time of patients with gemcitabine adjuvant chemotherapy was 22.1 months. These results support the use of gemcitabine as adjuvant chemotherapy in resectable pancreatic cancer.

The involvement of radiation as the adjuvant therapy for patients with resected pancreatic cancer has been discussed. The GITSG study showed the efficacy of chemoradiation as the adjuvant therapy.[12] Conversely, the recent ESPAC-1 study failed to show the efficacy of this therapy on postoperative survival, in contrast to chemotherapy alone.[17] In this study, although the local recurrence was most frequently observed, many of these patients also showed other types of recurrences at the same time. This may indicate that the effect of radiation therapy as the adjuvant therapy might be limited regarding the survival of patients with resected pancreatic cancer.

Interestingly, in this study there were no significant differences in disease-free and overall survival rates between N− and N+ patients and between R0 and R1 patients. Nodal status (N) and resection status (R) are usually considered prognostic factors for pancreatic cancer after resection.[31-33] However, the ESPAC-1 study also reported that patients with R1 resection also benefited from adjuvant chemotherapy.[31] These results may indicate that patients with N+ or R1 status benefit more from adjuvant chemotherapy using gemcitabine.

In conclusion, the present study did not demonstrate the efficacy of a UFT and gemcitabine combination as an adjuvant therapy for patients with resected pancreatic cancer compared with gemcitabine alone. It did, however, add further evidence that an adjuvant therapy using gemcitabine can produce favorable effects on the prognosis without any severe toxicity. This strongly suggests that further clinical trial resources for adjuvant chemotherapy should be addressed through the use of other combinations of agents with gemcitabine.

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