Gemcitabine Chemotherapy Versus 5-fluorouracil–based Concurrent Chemoradiotherapy in Locally Advanced Unresectable Pancreatic Cancer

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Objectives: The aim of this study was to compare the survival benefits associated with gemcitabine chemotherapy and 5-fluorouracil (5-FU)–based concurrent chemoradiotherapy (CCRT) in locally advanced unresectable pancreatic cancer.

Methods: One hundred and thirty-eight locally advanced unresectable pancreatic cancer patients were retrospectively enrolled from January 1995 to January 2005. All cases were histologically proven, and patients received gemcitabine chemotherapy, 5-FU–based CCRT, or supportive care at Seoul National University Hospital.

Results: Median overall survival was 8.2 months. Twenty-six patients received gemcitabine chemotherapy, 56 patients 5-FU–based CCRT, and 56 patients supportive care. Weight loss and treatment modality were identified as independent prognostic factors by multivariate analysis. Patients in the 5-FU–based CCRT (overall survival, 10.4 months) and gemcitabine chemotherapy (11.3 months) groups showed survival benefit over those received supportive care (6.1 months, $P < 0.0001$). No grades 3 to 4 toxic adverse effects occurred in either treatment group and no statistical significant survival difference was found between gemcitabine chemotherapy and 5-FU–based CCRT ($P = 0.5$).

Conclusions: Patients with locally advanced pancreatic cancer who received gemcitabine chemotherapy or 5-FU–based CCRT showed better survival than those who received supportive care only. Gemcitabine chemotherapy and 5-FU–based CCRT showed similar survival advantages.

Key Words: pancreatic cancer, chemotherapy, concurrent chemoradiotherapy, gemcitabine, survival

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Cancer of the exocrine pancreas remains a fatal disease for most patients because of its predominantly late diagnosis and poor response to nonsurgical treatment. Patients with resectable pancreatic cancer clearly represent a minority (10%–15%).[1–4] After surgical resection with or without adjuvant therapy, median survival is limited to a range of 11 to 23 months, and 5-year survival is approximately 20%.[2,4] Locally advanced nonmetastatic disease is observed in 15% to 20% of pancreatic cancer patients at initial diagnosis and is associated with a median survival of 6 to 10 months.[4–7] Patients with locally advanced carcinoma of the pancreas comprise an intermediate group. These patients have pancreatic tumors that are defined as surgically unresectable but have no evidence of distant metastases.[8–10] A tumor is considered to be unresectable if it has one of the following features: extensive peripancreatic lymph node involvement and/or distant metastases, encasement of occlusion of the superior mesenteric vein or superior mesenteric vein/portal vein confluence, or direct involvement of the superior mesenteric artery, celiac axis, inferior vena cava, or aorta.[8,11] In 1969, the Mayo Clinic randomized 64 patients to external beam radiotherapy plus 5-fluorouracil (5-FU) or radiotherapy alone, and observed an improved mean survival of 10.4 months for radiotherapy with 5-FU, compared with 6.3 months for radiotherapy alone.[12] Since then, this modality has been viewed as a standard therapy for locally advanced pancreatic cancer. The major obstacle in improving long-term survival is systemic failure. Moreover, because of high rates of distant metastases and poor overall survival (OS) results, some investigators have questioned the value of radiation therapy for the treatment of this patient subset.[7,8] After the introduction of gemcitabine therapy, Burris et al[13] compared the effectiveness of gemcitabine with that of 5-FU in locally advanced pancreatic cancer and in metastatic pancreatic cancer, and found a 4.41-month OS for 5-FU and a 5.65-month survival for gemcitabine.[13] However, both drugs had low response rates, that is, 5-FU had a 4.8% and gemcitabine a 23.8% "clinical benefit response", which was evaluated based on pain palliation, increased performance score, and weight gain. Eventually, gemcitabine became widely accepted for unresectable pancreatic cancer, but no comparative studies have been undertaken to compare gemcitabine chemotherapy and 5-FU–based concurrent chemoradiotherapy (CCRT) in locally advanced, unresectable pancreatic cancer. Moreover, if there is no survival difference or benefit of gemcitabine chemotherapy versus 5-FU–based CCRT, it could be more convenient and could improve the quality of life of locally advanced pancreatic cancer patients. Therefore, we compared the survival benefits and toxicities of gemcitabine chemotherapy and CCRT in locally advanced pancreatic cancer. In

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addition, we attempted to identify the clinical and laboratory prognostic factors that affect patient survival.

MATERIALS AND METHODS

Patients

The candidate subjects for this retrospective study were 353 histologically proven, unresectable pancreatic cancer patients, who registered at Seoul National University Hospital from January 1995 to January 2005. Locally advanced, unresectable pancreatic cancer was defined as described by the 6th American Joint Committee on Cancer stage III. We only included the pancreatic cancer patients who have 6th American Joint Committee on Cancer stage III at the time of diagnosis. In addition, we excluded the patients who have severe comorbidities (eg, severe congestive heart failure, other malignancy, and Child C liver cirrhosis) that could affect survival. Two hundred and fifteen patients (200 patients who were in stage IV, 15 patients who were in stage III but had severe comorbidities) were excluded from the total 353 pancreatic cancer patients. Finally, 138 histologically proven, locally advanced, unresectable pancreatic cancer patients who were followed up until December 2005 constituted the study cohort.

TABLE 1. Basal Characteristics of 138 Patients

Variables	No. Patients
Eligible patients	138
Age	
Median (range)	60 (28–87)
Sex	
M/F	93/45
Performance status	
ECOG 0–1	109
ECOG 0–2	22
ECOG 0–3	7
ECOG 0–4	0
Drain	
None	94
PTBD	17
ERBD	24
Bypass	3
Smoking	
No	64
Yes	41
Unknown	33
Weight loss	
None	26
1–5 kg	32
6–10 kg	34
>10 kg	14
Unknown	32
DM at diagnosis	
Yes	49 (35%)
At diagnosis	26
≤6 mo	7
6–12 mo	2
>12 mo	14
Tumor site	
Head	77 (56%)
Body	36 (26%)
Tail	25 (18%)
Jaundice	
Yes	45 (33%)
No	93 (67%)

ECOG indicates Eastern Cooperative Oncology Group; ERBD, endoscopic retrograde biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

TABLE 2. Multivariate Analysis for Overall Survival

		Hazard ratio (95% confidence interval)	*P*
Age (y)	28–51 (first tile)	1.0	0.243
	52–59 (second)	0.51 (0.25–1.00)	
	60–69 (third)	0.63 (0.34–1.12)	
	70–87 (fourth)	0.70 (0.38–1.30)	
Weight loss	None	1.0	0.007
	1–5 kg	0.87 (0.46–1.66)	
	6–10 kg	1.58 (0.88–2.86)	
	>10 kg	1.94 (0.87–4.33)	
Initial treatment modality	Supportive care	1.0	<0.001
	Gemzar chemotherapy	0.38 (0.21–0.69)	
	CCRT	0.38 (0.24–0.60)	

Treatment Modalities

Patients underwent gemcitabine chemotherapy, 5-FU–based CCRT, or supportive care. Because gemcitabine chemotherapeutic agent has been used widely as a chemotherapeutic in Korea from 1999, we were able to choose between 5-FU–based CCRT or best supportive care during the period 1995 to 1998, and from 1999 three options became available (5-FU–based CCRT, gemcitabine chemotherapy, and best supportive care). To determine individual treatment modality, patients were informed of the prognosis and of the effects of each treatment modality. Choices were made after thorough discussions between patients and physicians. Final decision was made by the patients and their family.

The 5-FU–based CCRT consisted of a 20-Gy dose to the tumor given in 10 daily fractions over a 2-week period plus an intravenous bolus of 5-FU (500 mg/m^2 of body-surface area on each of the first 3 days of radiotherapy and again after a planned break of 2 weeks). Adverse effects were assessed using World Health Organization (WHO) toxicity criteria. After completing the treatment protocol, computed tomography was performed 3 to 6 months to evaluate disease progression.

Gemcitabine (2,2-difluorodeoxycytidine, Gemzar; Eli Lilly and Co) 1000 mg/m^2 was administered as a 30-minute intravenous infusion once weekly for 3 of every 4 weeks at a dose of 1000 mg/m^2. If blood counts had not recovered to an absolute neutrophil count greater or equal to 1000 per microliter and platelet count greater or equal to 50,000 per microliter on the day of therapy, chemotherapy was omitted.

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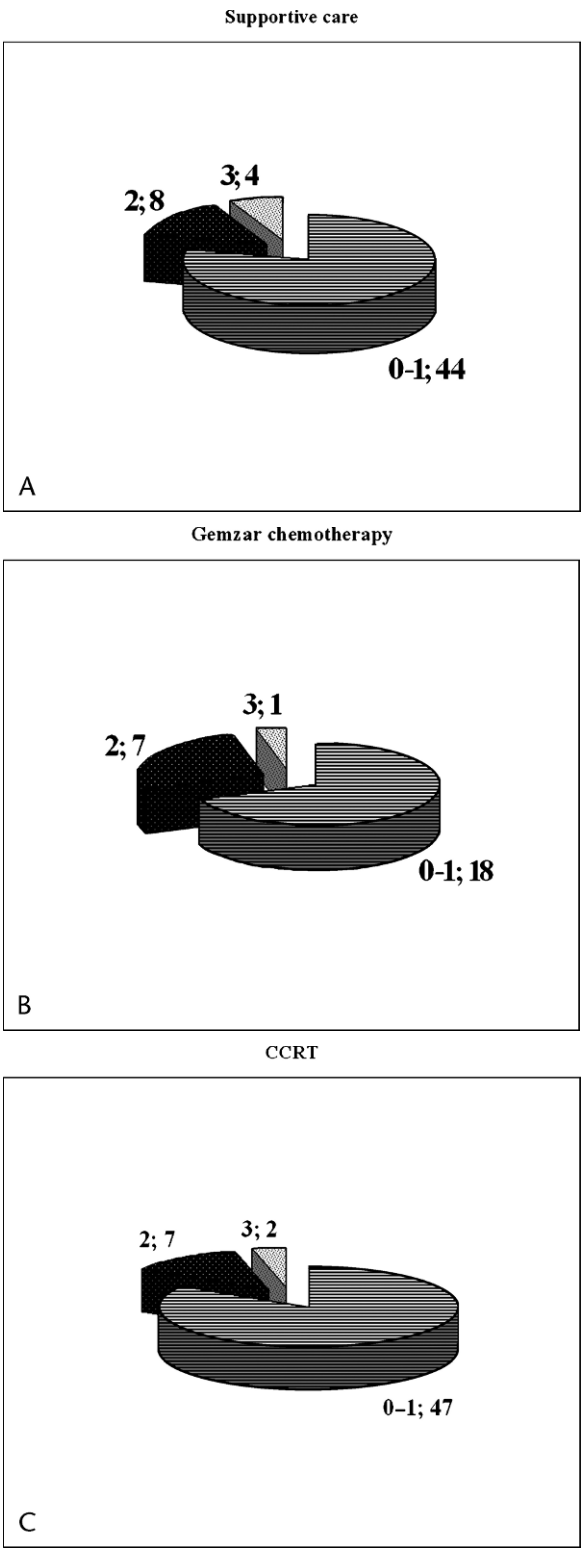

FIGURE 1. Performance status according to treatment modality. A, Supportive care. B, Gemcitabine chemotherapy. C, CCRT.

Adverse effects were assessed using WHO toxicity criteria. The dose of gemcitabine was reduced by 25% for all other grade 3 toxicities (except alopecia) and omitted for any grade 4 toxicity. Gemcitabine chemotherapy was performed until disease progression or a patient's general condition deteriorated. Computed tomography was performed 3 to 6 months to evaluate disease progression.

The patients who refused further chemotherapy or 5-FU–based CCRT treatment were assigned to the best supportive care group. They were treated to relieve pain, infection, obstruction, and provided psychological support as the cancer progressed.

Assessment

Unfortunately, our study was not of a randomized prospective design. Therefore, we tried to make 2 points clear before comparing survival rates in each different treatment modality group. First, we investigated the performance statuses of the patients according to treatment modalities. Second, because gemcitabine has been widely used as a chemotherapeutic from 1999, we compared survivals during the pregemcitabine era with those during the postgemcitabine era in the supportive care group to ensure that they were homogenous enough to exclude the possibility of selection bias.

In addition, we reviewed medical records thoroughly and investigated the following clinical and laboratory variables believed capable of affecting OS: age, sex, performance status, presence of diabetes mellitus (DM), time interval since DM, weight loss, tumor location (head, body, tail), total bilirubin level, initial Carbohydrate Antigen (CA) 19-9 level, drainage

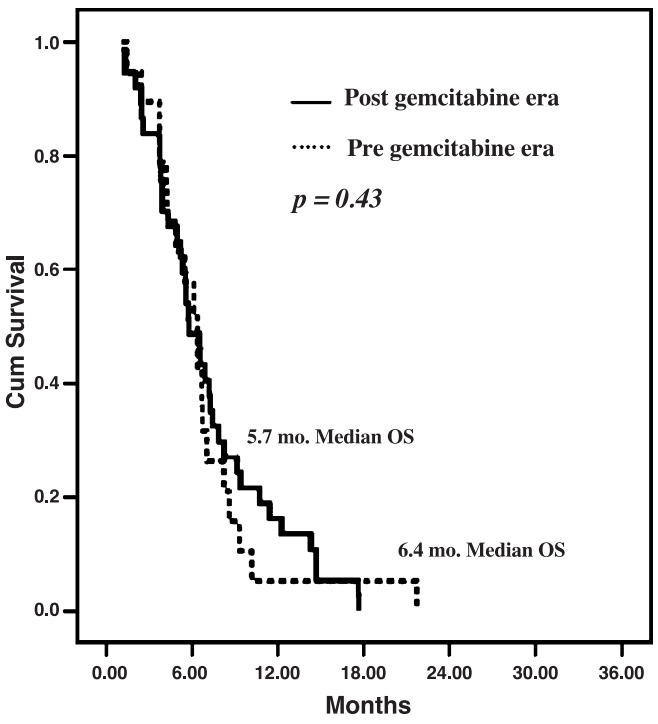

FIGURE 2. Comparison of OS between pregemcitabine versus postgemcitabine era in the supportive care group.

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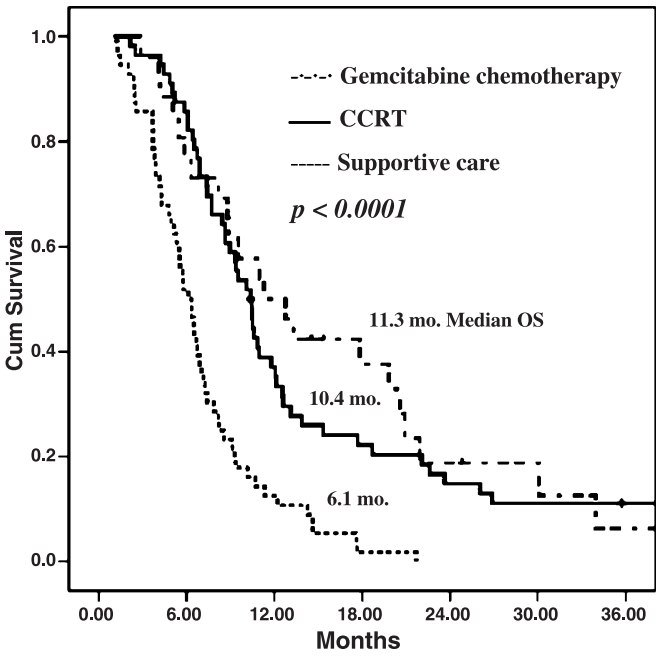

FIGURE 3. Survival curve according to treatment modality.

modality, smoking habits, and treatment modality. We defined weight loss as more than 10% of ideal body weight and checked absolute weights. Normal total bilirubin levels range from 0.2 to 1.2 mg/dL, and anything above 1.2 mg/dL was defined as jaundice. The normal CA 19-9 level range was taken to be from 0 to 37 U/mL. The survival data was collected by telephone interview and mail, and from National Statistical Office records.

Statistical Analyses

Survival curves were constructed by using the Kaplan-Meier method. Statistical analyses of categorical variables were performed using Pearson's χ^2 test or Fisher exact test; 2 level continuous variables and 3 or more level continuous variables were compared using the Student t test and analysis of variance, respectively. Two-sided P values of less than 0.05 were considered significant. All analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc, Chicago, Ill).

RESULTS

Patients' Characteristics

The basal characteristics of 138 patients are presented in Table 1. Mean patient age was 60 years (range, 28–87). Twenty-six patients (19%) had DM at the time of diagnosis, and 7 patients had DM 6 months before the diagnosis. Seventy-seven (56%) patients had a tumor in the pancreatic head and 45 patients (33%) had jaundice at the time of diagnosis.

The Prognostic Factors Affecting Overall Survival

Median OS was 8.2 months (95% confidence interval, 7.0–9.5), and univariate analysis showed that age, weight loss, and treatment modality were all statistically significant prognostic factors of OS. Performance status, presence of DM, and tumor site were not identified by univariate analysis as significant prognostic factors. However, multivariate analysis identified weight loss and treatment modality as the only independent prognostic factors (Table 2).

Overall Survival and Treatment Modalities

In each treatment modality, there was no statistical difference among the different performance status, and the P value was 0.31 (Fig. 1). In addition, no significant survival difference was observed between the pregemcitabine and postgemcitabine era in the supportive care group (Fig. 2). Twenty-six patients received gemcitabine chemotherapy alone, 56 patients received 5-FU–based CCRT, and 56 patients received supportive care. Patients who were administered with 5-FU–based CCRT (median OS, 10.4 months) or gemcitabine chemotherapy alone (median OS, 11.3 months) showed a survival benefit over supportive care only (median OS, 6.1 months, Fig. 3). In particular, no statistical significant difference was observed between the gemcitabine chemotherapy and 5-FU–based CCRT groups for survival (median OS, 11.3 vs 10.4 months; $P = 0.5$; Fig. 4).

Toxicity

No grades 3 to 4 toxic adverse effects were observed in either of the 2 treatment groups, and no patient was taken off

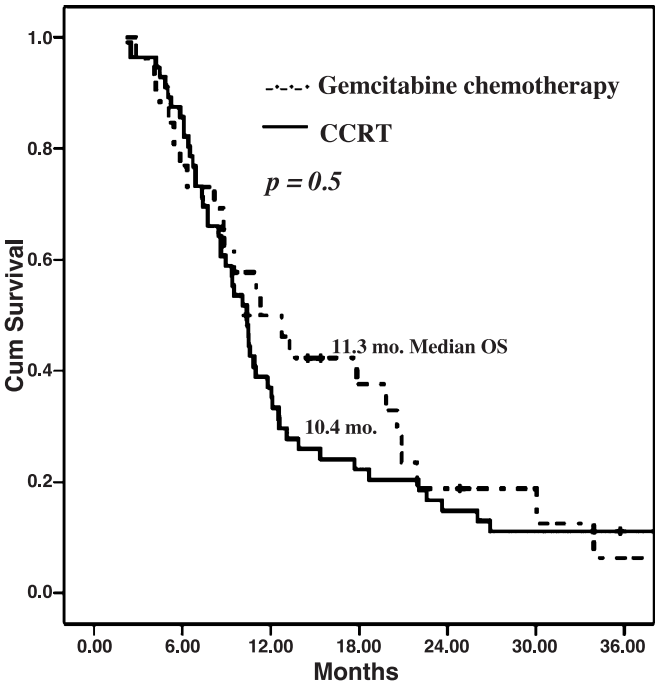

FIGURE 4. Comparison of survival between CCRT and gemcitabine chemotherapy.

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TABLE 3. Toxicity of 5-FU Concurrent Chemoradiotherapy and Gemcitabine Chemotherapy

	Grade (No. Patients)									
	5-FU–based CCRT					Gemcitabine Chemotherapy				
Toxicity (WHO)	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Nausea and vomiting	30	24	2	0	0	24	2	0	0	0
Stomatitis	45	11	0	0	0	26	0	0	0	0
Diarrhea	54	2	0	0	0	24	2	0	0	0
Leucopenia	45	6	5	0	0	18	6	2	0	0
Thrombocytopenia	56	0	0	0	0	26	0	0	0	0
Fever	53	3	0	0	0	20	4	1	0	0

the 5-FU–based CCRT or gemcitabine chemotherapy due to toxicity (Table 3). Seven of 56 patients experienced grade 2 toxic adverse effects in the 5-FU–based CCRT group and 3 of 26 patients in the gemcitabine chemotherapy group, which was not statistically significant ($P = 0.6$).

DISCUSSION

This study indicates that more active treatment should be attempted, even in the cases of locally advanced unresectable pancreatic cancer. In clinical practice, most clinicians have a tendency not to recommend an active treatment modality due to the poor prognosis of this disease, or because of patients' wishes or old age, although patients are in excellent medical condition. Krzyzanowska et al,[14] reporting on their locally advanced pancreatic cancer cohort study, found that 44% of patients received some form of cancer-directed therapy (24% radiation with CCRT, 13% radiation alone, and 7% chemotherapy alone). Furthermore, active treatment was found to be associated with several nondisease-related factors, that is, age, socioeconomic status, and region of residence.[14] Moreover, any kind of active treatment was found to prolong survival in their cohort study.[14] In the present study, multivariate analysis showed that age is not an independent prognostic factor of OS, which indicates that active treatment should not be pursued in the elderly. In addition, we found that in the 5-FU–based CCRT (median OS, 10.4 months) and the gemcitabine chemotherapy alone (median OS, 11.3 months) groups showed survival benefits over supportive care only (median OS, 6.1 months). Burris et al[13] reported a 5.7-month median OS in their gemcitabine chemotherapy group, which is lower than our finding, but they included patients with locally advanced and metastatic cancers. In addition, Klaassen et al[15] reported an overall median survival of 8.2 months in locally advanced, unresectable, pancreatic cancer patients without distant metastases who are treated with 5-FU CCRT or 5-FU–based chemotherapy. In the present study, we achieved an overall median survival of 8.2 months after including patients without active treatment (supportive care only group).

No significant survival difference was observed for 5-FU–based CCRT and gemcitabine chemotherapy. Moreover, gemcitabine chemotherapy did not cause any severe toxicity and would be more available for most pancreatic cancer patients. As we mentioned in "Results" above, we only observed grades 1 to 2 toxic adverse effects in groups treated with gemcitabine chemotherapy or 5-FU–based CCRT, and no significant difference was observed in grade 2 toxic adverse effects in these 2 groups ($P = 0.6$). Therefore, we could conclude that 5-FU–based CCRT and gemcitabine chemotherapy are both well tolerated. This result might be important, because the standard treatment remains 5-FU–based CCRT for patients with locally advanced, unresectable, pancreatic cancer.[6,10,11,16–19] Then, if the above results accurately reflect reality, what is the role of 5-FU–based CCRT in the treatment of locally advanced, unresectable, pancreatic cancer? Practically speaking, the 5-FU–based CCRT protocol requires that patients travel to a clinic every other day, and undergo radiotherapy, which is troublesome. However, gemcitabine chemotherapy offers no satisfactory additional beneficial effect in long-term survival. For this reason, many trials have compared gemcitabine single therapy versus gemcitabine combination therapy in advanced pancreatic cancer; summarizing these include gemcitabine versus gemcitabine plus cisplatin, gemcitabine versus gemcitabine plus continuous infusion 5-FU, and gemcitabine versus gemcitabine plus capecitabine. However, none of these combinatorial regimens produced a significant survival difference.[5,20] The most recent study was conducted by Louvet et al,[18] who compared gemcitabine versus gemcitabine in combination with oxaliplatin in locally advanced or metastatic pancreatic cancer in phase III trial. However, they obtained median survivals of 7.1 and 9.0 months, respectively, which was not significantly different ($P = 0.13$).[18] Overall, based on the results of the present study, it could be carefully recommended that gemcitabine chemotherapy has plenty of potentials to replace 5-FU–based CCRT in locally advanced, unresectable, pancreatic cancer. Nevertheless, should a well-tolerated chemotherapeutic be found with a definite survival or clinical benefit versus 5-FU–based CCRT, the treatment strategies should be changed. Gemcitabine-based CCRT has been suggested to improve survival. Blackstock et al[21] reported on a phase I trial of twice-weekly gemcitabine and concurrent radiation in patients with advanced pancreatic cancer. However, although their regimen was well tolerated and may have significant activity, the optimal dose of gemcitabine with radiotherapy has still not been defined, nor is it known whether this regimen is superior to 5-FU chemoradiotherapy.[18,21,22]

The present study has some limitations that should be borne in mind. First, the gemcitabine chemotherapy group contained only 26 patients whereas the 5-FU–based CCRT group had 56. Second, this was a retrospective study and thus could be subject to group selection bias. However, we tried to minimize selection bias and to overcome the limitations of this retrospective study. As we mentioned in the "Methods" section, we compared the difference among the performance status according to the treatment modality and the survival difference between pregemcitabine and postgemcitabine era in the supportive care group, and found no statistically significant difference.

In addition, 6 patients survived for more than 36 months after diagnosis; 5 patients in the 5-FU–based CCRT group

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and 1 patient in the gemcitabine chemotherapy group, and 2 patients remain alive. One of these patients was from the 5-FU–based CCRT group and had stable disease at the last follow-up. The other patient was in the gemcitabine chemotherapy group and was in partial remission at the last outpatient clinic. Carpelan-Holmstrom et al,[23] in a nationwide study, re-evaluated the data of the Finnish cancer registry, which contained 89 pancreatic ductal adenocarcinoma patients, regardless of staging, who had survived for more than 5 years. However, after the re-evaluating pathology slides, it was found that only 26 of these patients (29%) had a correct diagnosis.[23] Although they had the patients with stage below IIB, we realized that the percentage of correct pathological results are too low and need to be confirmed. Therefore, we re-evaluated the slides and paraffin blocks in the pathology department at Seoul National University Hospital. All were pancreatic ductal adenocarcinoma, and no mistake was found in clinical staging or survival data. However, these long surviving patients need to be investigated and categorized for tailored therapy in the future.

In conclusion, the present study shows that gemcitabine chemotherapy offers a survival advantage similar to that of 5-FU–based CCRT in patients with locally advanced pancreatic cancer. However, the roles of different treatment modalities require further prospective randomized investigation to identify optimal treatment modalities.

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