

Clinical Investigation: Gastrointestinal Cancer

# Concurrent Radiotherapy and Gemcitabine for Unresectable Pancreatic Adenocarcinoma: Impact of Adjuvant Chemotherapy on Survival

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## Summary

This retrospective study looked at patients with unresectable pancreatic cancer treated with different combinations of chemotherapy and radiation. When concurrent chemo-radiotherapy using gemcitabine was used, a relatively favorable local control rate was seen. When adjuvant chemotherapy was given,

**Purpose:** To retrospectively analyze results of concurrent chemoradiotherapy (CCRT) using gemcitabine (GEM) for unresectable pancreatic adenocarcinoma.

**Methods and Materials:** Records of 108 patients treated with concurrent external beam radiotherapy (EBRT) and GEM were reviewed. The median dose of EBRT in all 108 patients was 50.4 Gy (range, 3.6–60.8 Gy), usually administered in conventional fractionations (1.8–2 Gy/day). During radiotherapy, most patients received GEM at a dosage of 250 to 350 mg/m<sup>2</sup> intravenously weekly for approximately 6 weeks. After CCRT, 59 patients (54.6%) were treated with adjuvant chemotherapy (AC), mainly with GEM. The median follow-up for all 108 patients was 11.0 months (range, 0.4–37.9 months).

**Results:** Initial responses after CCRT for 85 patients were partial response: 26 patients, no change: 51 patients and progressive disease: 8 patients. Local progression was observed in 35 patients (32.4%), and the 2-year local control (LC) rate in all patients was 41.9%. Patients treated with total doses of 50 Gy or more had significantly more favorable LC rates (2-year LC rate, 42.9%) than patients treated with total doses of less than 50 Gy (2-year LC rate,

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a small survival benefit became evident. Adjustments in the sequencing of chemotherapy and radiation thus have the potential to improve outcomes.

29.6%). Regional lymph node recurrence was found in only 1 patient, and none of the 57 patients with clinical N0 disease had regional lymph node recurrence. The 2-year overall survival (OS) rate and the median survival time in all patients were 23.5% and 11.6 months, respectively. Patients treated with AC had significantly more favorable OS rates (2-year OS, 31.8%) than those treated without AC (2-year OS, 12.4%;  $p < 0.0001$ ). On multivariate analysis, AC use and clinical T stage were significant prognostic factors for OS.

**Conclusions:** CCRT using GEM yields a relatively favorable LC rate for unresectable pancreatic adenocarcinoma, and CCRT with AC conferred a survival benefit compared to CCRT without AC. © 2012 Elsevier Inc.

**Keywords:** Chemotherapy, Gemcitabine, Pancreatic neoplasms, Radiotherapy, Unresectable

## Introduction

Pancreatic cancer is one of the leading causes of cancer death worldwide. The prognosis for patients with this disease remains extremely poor, with a 5-year survival rate after diagnosis of less than 5% (1, 2). Most patients with pancreatic cancer already have advanced disease at the time of diagnosis, and among patients with unresectable pancreatic cancer, nearly half of patients have advanced but localized disease (2).

In the 1980s, the Gastrointestinal Tumor Study Group reported the survival benefit of 5-fluorouracil (5-FU)-based concurrent chemoradiotherapy (CCRT) over that of external beam radiotherapy (EBRT) alone in patients with unresectable pancreatic cancer (3). Until recently, CCRT has been the standard approach to treating surgically unresectable, localized disease. More recently, therapy using the drug gemcitabine (GEM), a nucleoside analogue, has been reported to confer marginally superior clinical benefit and survival compared with that with 5-FU (4). GEM has also been shown to be a potent radiosensitizer in pancreatic cancer (5). Therefore, concurrent radiotherapy and GEM may be a promising strategy for treating unresectable localized pancreatic cancer. However, optimal management of concurrent EBRT and GEM for unresectable disease has not been fully investigated.

In the current study, we reviewed a retrospective and multi-institutional series of 108 patients with nonmetastatic unresectable pancreatic cancer, who were treated with concurrent radiotherapy using GEM, and evaluated the efficacy and safety of this treatment for these tumors.

## Methods and Materials

The Japanese Radiation Oncology Study Group (JROSG) conducted a nationwide questionnaire survey of patients with non-metastatic pancreatic adenocarcinoma who were treated with radiotherapy. The questionnaire elicited detailed information regarding patient characteristics, treatment characteristics, and outcomes of treatments. Details of the JROSG survey have been described elsewhere (6–8). Briefly, 34 radiation oncology centers belonging to the JROSG agreed to participate in this survey, and detailed information for 870 patients was accumulated. Of these patients, 223 patients with unresectable disease were treated with concurrent EBRT and GEM. Histology finding for 108 patients was adenocarcinoma; 3 patients had other histological findings, such as anaplastic carcinoma and undifferentiated carcinoma; and 112 patients had no histological information. These last 115

patients were excluded from this study, and the remaining 108 patients with histological diagnosis of adenocarcinoma were the subjects of the current study. Their tumors were judged to be unresectable by the respective physicians at each institution. Of these 108 patients, there were 3 patients with inoperable cancer, who were not fit for surgery, and the remaining 105 patients had unresectable tumors at presentation.

Patient and treatment characteristics for all 108 patients are shown in Table 1. The median age of patients was 63 years old (range, 40–83 years old), and the Eastern Cooperative Oncology Group (ECOG) performance status (PS) ranged from 0 to 3 (median, 1). We used the tumor staging system devised by the Union Internationale Contre le Cancer (9). The median maximum tumor size was 3.9 cm (range, 1.4–10.0 cm), and the median serum concentration of carbohydrate antigen 19-9 (CA19-9) was 511 U/mL (range, 0–57,300 U/mL). Total doses of EBRT ranged from 3.6 to 60.8 Gy (median, 50.4 Gy), with a single fraction of 1.8 to 2 Gy given 5 days per week in most patients. On the other hand, 11 patients (10.2%) were treated with a single fraction of 2.2 to 2.5 Gy.

Chemotherapy schedules are described in Table 2. During radiotherapy, 8 patients received a dosage of 1,000 mg/m<sup>2</sup> GEM weekly for 3 weeks with a 1-week rest period, depending on their response and toxicity (using the standard dosage of GEM). The remaining 100 patients received GEM at a dosage of 250 to 350 mg/m<sup>2</sup> intravenously weekly during radiotherapy for approximately 6 weeks (low-dose GEM). After radiotherapy, 59 of 108 patients (54.6%) were treated with adjuvant chemotherapy (AC). Fifty-three of 59 patients (89.8%) received GEM maintenance chemotherapy, usually given at 1,000 mg/m<sup>2</sup> weekly for 3 weeks with a 1-week rest period, until disease progression or unacceptable toxicity was reached. Six patients received intravenous bolus infusions of 300 to 500 mg/m<sup>2</sup> 5-FU, until disease progression or unacceptable toxicity was reached. For 5 patients, a combination compound of tegafur, 5-chloro-2, 4-dihydropyridine, and oteracil potassium (S-1) was administered orally, and S-1 doses ranged from 50 to 80 mg/m<sup>2</sup>.

In the current study, there were no definitive treatment policies for pancreatic cancer during the survey period; thus, treatment was determined by the respective physicians at each institution. We assigned 108 patients to two groups (patients treated with AC and those without AC treatment) and determined whether the AC influenced patient characteristics, such as age, tumor size, and clinical stage. There were no significant differences in age, gender, tumor site, tumor size, or clinical T stage and clinical N stage, except for CA19-9 levels, which varied according to the AC used (data not shown). Concerning PS, there were no significant differences according to the AC used, and 56 of 58 patients with

**Table 1** Patient and disease characteristics

Characteristic	No. of patients	% of total
Age (median, 63 years old)		
<70	84	77.8
≥70	24	22.2
Gender		
Female	50	46.3
Male	58	53.7
Primary site		
Head	55	50.9
Body	48	44.4
Tail	4	3.7
Unknown	1	0.9
Maximum tumor size (median, 3.9 cm)		
<4.0 cm	48	44.4
≥4.0 cm	54	50.0
Unknown	6	5.6
ECOG performance status scale		
0	28	25.9
1	70	64.8
2	5	4.6
3	1	0.9
Unknown	4	3.7
CA19-9 (U/ml) (median, 248.2 U/ml)		
<1,000	56	51.9
≥1,000	43	39.8
Unknown	9	8.3
Clinical T stage (UICC 2002)		
2	3	2.8
3	15	13.9
4	90	83.3
Clinical N stage (UICC 2002)		
0	57	52.8
1	49	45.4
Unknown	2	1.8
EBRT total radiation dose (Gy) (median, 50.4 Gy)		
<40	6	5.6
40 ≤ to <50	9	8.3
50 ≤ to <60	89	86.4
≥60	4	3.7
Dose per fraction (Gy)		
1.8–2	97	89.8
2.2–2.5	11	10.2
Radiation field		
Primary plus LN	65	60.2
Primary only	43	39.8
CT-based treatment planning		
Yes	106	98.1
No	2	1.9
Conformal therapy		
Yes	91	84.3
No	17	15.7
GEM dose during EBRT		
Low dose (250–350 mg/m <sup>2</sup> /week)	100	92.6
Standard dose (1,000 mg/m <sup>2</sup> /week)*	8	7.4

(continued)

**Table 1** (continued)

Characteristic	No. of patients	% of total
Adjuvant chemotherapy use		
Yes	59	54.6
No	49	45.4

Abbreviations: CA19-9 = carbohydrate antigen 19-9; CT = computed tomography; EBRT = external beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; GEM = gemcitabine; LN = lymph nodes; UICC = Union Internationale Contre le Cancer.

\* Usually administered weekly for 3 weeks with a 1-week rest period.

AC therapy (96.6%) and 42 of 46 patients without AC (91.3%) had PS of 0 to 1 ( $p = 0.2543$ ).

The median follow-up for all 108 patients was 11.0 months (range, 0.4–37.9 months). In the current study, local failure was defined as apparent primary tumor progression detected by computed tomography (CT) scans after CCRT. Assessment of initial response by CCRT was based on CT scans that were obtained within 3 months after CCRT. In the current study, complete response was defined as the complete disappearance of all visible tumor, and partial response (PR) was defined as a reduction of 50% to 99% in the product of the perpendicular diameters of the contrast-enhancing tumor. Progressive disease was defined as an increase of more than 25% in the product of the perpendicular diameters of the contrast-enhancing tumor or any new tumor seen on CT scans, and all other situations were defined as no change (NC). Overall survival (OS), progression-free survival (PFS), and local control (LC) rates were calculated actuarially according to the Kaplan-Meier method (10) and were measured starting from the day of initial treatment. Differences between groups were estimated using the chi-square test, Student's  $t$  test, and the generalized Wilcoxon test (11). Multivariate analysis was performed using the Cox regression model (12). A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed using SPSS software (version 11.0; SPSS, Inc., Chicago, IL). Acute and late adverse effects were graded in accordance with the National Cancer Institute-Common Terminology Criteria (NCI-CTC) version 3.0.

## Results

Data regarding initial responses after CCRT were available for 85 patients (Table 3). Of the 3 patients with inoperable tumors, 1 patient had a response of NC, and there was no information regarding tumor responses for the remaining 2 patients. At the time of this analysis, 95 patients (88.0%) had disease recurrence (local only in 29 patients; regional lymph nodes only in 1 patient; liver only in 24 patients; peritoneum only in 27 patients; and other distant metastases, such as at bone or lung, only in 4 patients; and multiple sites in 10 patients). Among the 10 patients with multiple recurrences, 6 patients had simultaneous local recurrences. Therefore, local recurrences occurred in a total of 35 patients (32.4%). The 2-year actuarial LC rate for all 108 patients was 41.9%. Figure 1 shows the LC curves according to the total radiation dose. Patients treated with a total dose of 50 Gy or more

**Table 2** Agents and chemotherapy schedules

Drug	No. of patients receiving a drug*	
	During RT	After RT
GEM	108	53 <sup>†</sup>
5-FU	—	6 <sup>†</sup>
S-1	—	5 <sup>†</sup>

Abbreviations: 5-FU = 5-fluorouracil; GEM = gemcitabine; RT = radiotherapy; S-1 = combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and oteracil potassium.

\* A total of 108 patients (100%) received a drug during RT, and 59 patients (54.6%) received a drug after undergoing RT.

<sup>†</sup> When combination chemotherapy was used, each drug in the combination was counted.

had a significantly more favorable LC rate (2-year LC rate, 42.9%) than patients treated with a total dose of less than 50 Gy (2-year LC rate, 29.6%;  $p = 0.0292$ ). Concerning the regional lymph node recurrence, all 57 patients with clinical stage N0 disease had no regional lymph node recurrence, and only 1 of 49 patients with clinical N1 disease had regional lymph node recurrence.

Eighty-seven of 108 patients (84.5%) died during the period of this analysis. Of these 87 patients, 85 patients died of pancreatic cancer, and the remaining 2 patients died without any sign of clinical recurrence (both of these patients died of intercurrent disease). The 2-year actuarial PFS rate and the median time to progression for all 108 patients were 8.2% and 6.0 months, respectively. Concerning AC use, the 2-year PFS rates for patients treated with AC (10.8%) were significantly higher than those for patients treated without AC (7.8%;  $p = 0.0187$ ). Univariate analysis showed that AC used, clinical T stage, and CA19-9 levels had a significant impact on PFS outcomes, and multivariate analysis showed that AC use and clinical T stage were significant prognostic factors (data not shown).

The 2-year actuarial OS rate and median survival time (MST) in all 108 patients were 23.5% and 11.6 months, respectively. Concerning AC use, 2-year OS rates for patients treated with AC (31.8%) were significantly higher than those for patients treated without AC (12.4%;  $p = 0.0022$ ) (Fig. 2). Univariate analysis showed that AC use, clinical T stage, and CA19-9 levels had a significant impact on OS outcomes (Table 4). However, when we excluded patients with hyperbilirubinemia (more than 2 mg/dl), CA19-9 concentration was not a significant factor for OS, and the 2-year OS rate was 27.4% in patients with CA19-9 concentrations <1,000 U/ml and 24.8% in patients with CA19-9 concentrations  $\geq$ 1,000 U/ml ( $p = 0.7104$ ). Multivariate analysis showed that the

use of AC (relative risk, 2.475; 95% confidence interval [CI], 1.564–3.917;  $p < 0.001$ ) and clinical T stage (relative risk, 0.374; 95% CI, 0.202–0.692;  $p = 0.002$ ) were significant prognostic factors. Other factors, such as CA19-9 level, tumor size, and total radiation dose did not influence OS outcomes.

In the current study, there were significant differences in the frequencies of AC use according to the initial response ( $p < 0.0001$ ) (Table 3), and patients with favorable responses had more frequently received AC than those with unfavorable responses. Therefore, we conducted subgroup analyses of OS according to initial responses. Concerning patients with an NC response, there was a significant survival benefit with AC use. On the other hand, patients with PR and those with progressive disease response had no significant survival benefit with AC use (Table 3).

Concerning adverse acute effects, 46 patients (42.6%) had Grade 3 to 4 leukopenia, 38 patients (35.2%) had Grade 3 to 4 appetite loss, and 16 patients (14.8%) had Grade 3 to 4 vomiting. Late adverse effects of Grade 3 or higher were observed in 1 patient (1.0%; Grade 3 gastrointestinal bleeding). Total radiation dose given to this patient was 50 Gy.

## Discussion

The current study indicated that CCRT using GEM yields noticeably favorable LC for unresectable pancreatic cancer, with a 2-year LC rate of 41.9%. Concerning initial responses of the 85 available patients, 27 patients (31.8%) had PR, 50 patients (58.8%) had NC response, and only 8 patients (9.4%) had progressive disease response. Several other reports also have indicated the efficacy of EBRT plus GEM therapy for LC (13, 14). Mattiucci *et al.* (13) treated 40 patients with unresectable pancreatic cancer with CCRT using GEM (1,000 mg/m<sup>2</sup>), and the 2-year LC rate was 39.6% (13). Yamazaki *et al.* (14) indicated that locoregional progression was observed in only 5 of 13 patients with unresectable tumors treated with EBRT plus GEM (14). These results indicate that CCRT using GEM produces relatively favorable LC for patients with unresectable tumors.

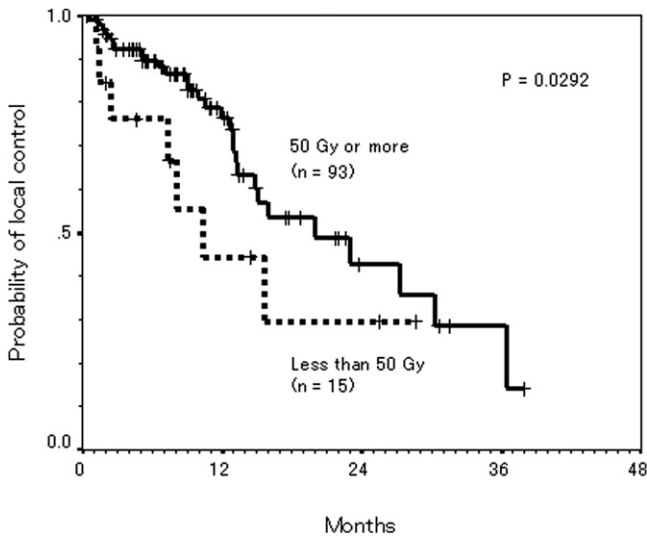
Although the efficacy of CCRT using GEM produces relatively favorable LC, optimal use of EBRT, that is, factors such as total radiation doses and radiation field, has not been clarified. National Comprehensive Cancer Network (NCCN) guidelines have recommended that for primary definitive chemoradiotherapy, total doses of 50 to 60 Gy (1.8–2.0 Gy/day) should be administered (15). Several investigators report using total doses of approximately 50 Gy for these tumors when GEM is combined with radiotherapy (13, 14, 16). In the current study, patients treated with total doses of

**Table 3** Comparisons of initial responses and overall survival according to AC use

Initial response	Total no. of patients	No. of patients			2-year OS rate (%)		
		AC (+)	AC (–)	$p$ value	AC (+)	AC (–)	$p$ value*
PR	26	25	1	<0.0001	25.3	0	0.3560
NC	51	24	27		34.3	12.1	<b>0.0251</b>
PD	8	2	6		0	0	0.7423
Unknown	23	8	15		—	—	—
Total	108	59	49		—	—	—

Abbreviations: AC (+) = with adjuvant chemotherapy; AC (–) = without adjuvant chemotherapy; NC = no change; OS = overall survival; PD = progressive disease; PR = partial response.

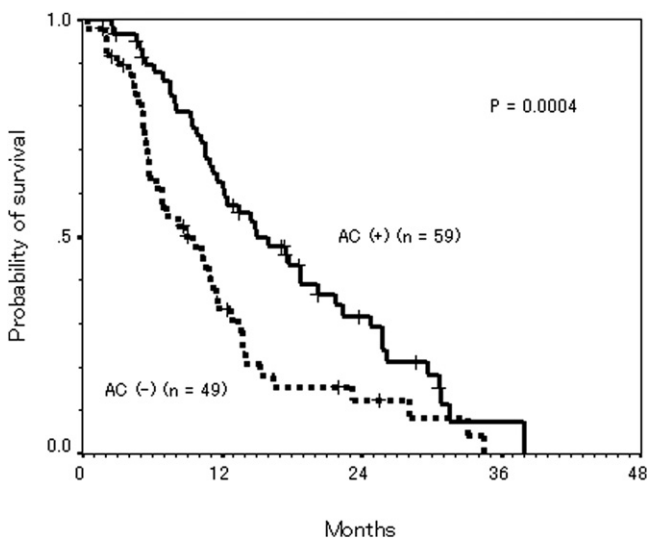
\*  $p$  value in boldface type indicates significant difference.



**Fig.1.** LC curves derived according to the total radiation dose in patients with unresectable pancreatic cancer are shown.

50 Gy or more had a significantly favorable LC rate (2-year LC rate, 42.9%) compared to patients treated with total doses of less than 50 Gy (2-year LC rate, 29.6%). These results suggest that doses of 50 Gy or more are appropriate for these tumors.

Concerning radiation fields, NCCN practice guidelines have also recommended that when 5-FU-based chemoradiotherapy is used, treatment volumes should include the primary tumor location and regional lymph nodes (15). When GEM is added, some authors have used the radiation field encompassing the primary tumor along with regional lymph nodes for treating these tumors (13, 16). Recently, other investigators have tried to irradiate only the primary tumor site in order to reduce radiation volume, especially to the intestine (14, 17). Murphy *et al.* (17) indicated that in conjunction with full-dose GEM, the use of conformal fields encompassing only the gross tumor volume (GTV) does not result in marginal failures. In the current study, regional lymph node recurrence was found in only 1 patient (0.9%), and none of



**Fig.2.** Actuarial OS curves according to administration of AC in patients with unresectable pancreatic cancer are shown.

the 57 patients with clinical N0 disease had regional lymph node recurrence. Therefore, when GEM is combined with radiation therapy, the treatment of choice may be to irradiate only the field of the primary tumor, especially for patients with stage N0 tumors. Further studies are required to confirm whether radiation only to the primary tumor field would be sufficient when CCRT with GEM is used.

When GEM is used as a single agent for treating patients with advanced cancer, the standard weekly dosage is approximately 1,000 mg/m<sup>2</sup>, and this dosage is regarded as necessary to control occult distant metastases (4). Therefore, considering both the metastasis-prone and the radio-resistant nature of pancreatic cancer, CCRT using full-dose radiotherapy (50 Gy or more) and full-dosage GEM (1,000 mg/m<sup>2</sup> weekly) appears to produce the best outcome. Yamazaki *et al.* (14) indicated that when limited-field 50-Gy radiotherapy was applied, concurrent administration of 1,000 mg/m<sup>2</sup> GEM was safe for these patients. Murphy *et al.* (17) indicated that when conformal fields encompassing only the GTV were applied, CCRT with 1,000 mg/m<sup>2</sup> GEM was safe (17). On the other hand, several reports have pointed out that CCRT with 1,000 mg/m<sup>2</sup> GEM may be too toxic in clinical practice (18, 19). Crane *et al.* (18) indicated that patients receiving GEM-based CCRT developed significantly more severe acute toxicity during treatment than patients receiving 5-FU-based CCRT. Therefore, in order to reduce severe acute toxicity, several researchers conducted studies of CCRT using low-dose GEM (15, 18, 20–22). Shibuya *et al.* (19) conducted a phase II trial of radiotherapy (54 Gy in 28 fractions) with weekly administration of GEM (250 mg/m<sup>2</sup>) and reported safe and promising results with a median survival time of 16.6 months and an acceptable level of toxicity (19). Huang *et al.* treated 55 patients with unresectable pancreatic cancer with concurrent 50.4-Gy EBRT and GEM, 400 mg/m<sup>2</sup> weekly, and found that this regimen can be safely administered (20). Further studies are required to investigate the optimal use of GEM for unresectable tumors.

Although CCRT using GEM provides relatively favorable LC rates, the role of this treatment in survival for these patients remains controversial. Several reports have indicated that when CCRT with GEM was administered, the 2-year OS rates and MSTs ranged from 11% to 25% and 10 to 16.6 months, respectively (13–20). In the current study, the 2-year actuarial OS rate and the median MST for all 108 patients were 23.5% and 11.6 months, respectively. These results indicate that despite the use of GEM, treatment outcomes are generally unfavorable for patients with these tumors. Therefore, it is important to investigate possible factors affecting the prognosis for patients treated with CCRT using GEM.

Several previous studies have suggested potential prognostic factors associated with PS and CA19-9 levels when CCRT is combined with GEM (20, 21). Recently, changes in CA19-9 levels after CCRT have emerged as a predictor for OS in patients with unresectable tumors (22). In the current study, we could not analyze changes in CA19-9 levels after CCRT due to limited information; however, it will be worthwhile to investigate more detailed analysis of CA19-9 levels in future studies. Our results indicated that AC use and clinical T stage were independent prognostic factors for OS. Several phase studies have used AC as a part of GEM-based CCRT (14, 20), and NCCN guideline recommend that (GEM-based) AC should be considered for patients with locally advanced disease who are receiving CCRT (15). Our results also indicated that CCRT with GEM-based AC conferred a survival benefit compared to CCRT without AC, and

**Table 4** Analysis of prognostic factors for OS in patients with unresectable pancreatic cancer treated with CCRT

Factor	No. of patients	Univariate analysis	
		2-y OS rate (%)	<i>p</i> value <sup>†</sup>
Age (years)			
<70	84	22.8	0.9265
≥70	24	27.1	
Gender			
Female	50	28.1	0.7141
Male	58	18.7	
Primary site			
Head	55	30.3	0.8527
Body/tail	52	16.0	
Maximum tumor size			
<4.0 cm	48	31.0	0.6200
≥4.0 cm	54	23.0	
ECOG performance status scale			
0–1	98	21.6	0.7728
2–3	6	33.3	
CA19-9 level (U/ml)			
<1,000	56	24.5	<b>0.0135</b>
≥1,000	43	20.8	
Clinical T stage (UICC 2002)			
2–3	18	41.0	<b>0.0044</b>
4	90	20.0	
Clinical N stage (UICC 2002)			
0	57	22.9	0.1377
1	49	22.9	
EBRT dose (Gy)			
<50	15	17.8	0.1624
≥50	93	24.6	
Radiation field			
Primary plus LN	65	20.5	0.4224
Primary only	43	27.1	
GEM dose during EBRT			
Low dose (250–350 mg/m <sup>2</sup> /week)	100	24.3	0.3199
Standard dose (1,000 mg/m <sup>2</sup> /week*)	8	0	
Adjuvant chemotherapy used			
Yes	59	31.8	<b>0.0004</b>
No	49	12.4	

Abbreviations: CA19-9 = carbohydrate antigen 19-9; CCRT = concurrent chemoradiotherapy; EBRT = external beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; GEM = gemcitabine; LN = lymph nodes; OS = overall survival; UICC = Union Internationale Contre le Cancer.

\* Usually administered weekly for 3 weeks with a 1-week rest period.

<sup>†</sup> *p* values in boldface type indicate significant difference.

subgroup analysis indicated that patients with a response of NC had significant clinical benefit with AC use. The possible reason for the clinical benefit of AC may be that AC delays the progression of residual primary tumor and/or development of distant metastasis. Therefore, from our results, AC should be administered after GEM-based CCRT, especially for patients with a response of NC. In the current study, 53 of 59 patients (89.8%) received GEM maintenance chemotherapy, usually given at

1,000 mg/m<sup>2</sup> weekly for 3 weeks with a 1-week rest period, and this regimen may be an attractive regimen for AC!! therapy. Further studies are required to investigate the optimal regimen of AC for these tumors.

## Conclusions

In conclusion, our results indicated that CCRT using GEM had a relatively favorable LC rate for unresectable pancreatic adenocarcinoma. Our results also indicated that CCRT in addition to AC conferred survival benefit compared to CCRT without AC. Because CCRT using GEM can achieve relatively favorable LC and the addition of AC increased the OS, CCRT using GEM combined with AC appears to be an attractive strategy for treating patients with unresectable tumors. However, this study is a retrospective study with various treatment modalities, and further prospective studies are required to confirm our results.

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