Concurrent Chemoradiotherapy with or without Induction Chemotherapy *versus* Chemotherapy Alone in Patients with Locally Advanced Pancreatic Cancer

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Abstract. *Background/Aim: The role of chemoradiotherapy (CRT) in the management of locally advanced pancreatic cancer is controversial. We aimed to explore this issue by retrospectively comparing the efficacy of concurrent CRT with or without induction (CT) versus CT alone in patients with locally advanced pancreatic cancer (LAPC). Patients and Methods: Between January 2006 and December 2012, 55 patients with biopsy-proven LAPC were treated either with CRT (n=31) or CT alone (n=24) at the authors' Institution. CT before or after CRT were allowed. Radiation therapy was delivered with a median dose of 50.4 Gy in a single fraction of 1.8 Gy and concurrent CT was typically given with gemcitabine at a dose of 400 mg/m^2 weekly. The majority of CT was gemcitabine-based (96%). Progression-free survival and overall survival were calculated from the date of diagnosis to the date of progression and to the date of death or last follow-up, respectively. Results: Patients' characteristics were not significantly different between the CRT group and CT-alone group. Nineteen (61%) patients received scheduled radiation dose of 50.4 Gy. The median cumulative dose of maintenance CT with gemcitabine after CRT was 6,500 mg/m^2. The median survival was 14.6 versus 8.1 months (p=0.001) and progression-free survival was 8.7 versus 4.9 months (p<0.001) for the CRT group and CT-alone group, respectively. Conclusion: Patients with LAPC treated with CRT conferred more favorable survival than those who did not receive CRT. CRT should be considered integrating into the management of LAPC.*

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Pancreatic cancer is the eighth leading cause of cancer death in Taiwan with overall 5-year survival rates of <10% (1). At initial diagnosis, nearly half of the patients with pancreatic cancer have metastatic disease and 30-40% of patients present with locally advanced disease, which precludes surgical resection (2). Locally advanced pancreatic cancer (LAPC), defined as unresectable disease with local vascular invasion without detectable metastases, has been challenging for the dismal survival outcome ranging from 8 to 13 months (3, 4). Locoregional progression and distant metastases *via* lymphatic and hematogeneous spread continue to be an obstacle for better outcomes.

Optimal treatment for LAPC remains controversial. Upfront chemoradiotherapy (CRT) in combination with 5-fluorouracil (5-FU) or gemcitabine-based chemotherapy (CT) has been commonly adopted in clinical practice (5-9). CT alone is an increasingly utilized strategy for patients with LAPC and supported by CT trials conducted in mixed populations of patients with metastatic and locally advanced disease (10-12). Ishii *et al*. reported a comparable survival of 15 months in a phase II study of 50 Japanese patients with LAPC treated with gemcitabine alone (13). Few trials attempt to directly compare primary CRT with CT alone, while none could draw a conclusion (5, 14, 15). In the French FFCD-SFRO trial (14), 119 patients with LAPC treated with CT alone had better survival than CRT. The second study, ECOG 4201, demonstrated a survival benefit of radiotherapy (RT) integrated into CT alone (15).

The use of induction CT followed by CRT for patients with no evidence of progression, increased at many Institutions, represented the paradigm shift over the past 5 years (4, 16-18). The rationale was based on selection of a subgroup of patients with LAPC who harbor more localized

biology and may derive a survival benefit from additional CRT. The use of induction CT indicates a way to identify patients more likely to benefit from CRT. To date, the benefit of delayed CRT strategy was from a retrospective analysis with inherent limitation. It is an important question required to answer whether CRT should be a component of treatment of LAPC or systemic CT alone is adequate.

Herein we report on the results of a retrospective analysis of CT alone *versus* CRT for patients with LAPC. We aimed to investigate whether there was a role of CRT in the multidisciplinary management of patients with LAPC.

Patients and Methods

Patient population. This retrospective study included patients with histologically- or cytologically-confirmed ductal adenocarcinoma between January 2006 and December 2012. Locally advanced unresectable disease was defined by the consensus from the guideline of the National Comprehensive Cancer Network (19). Patients with metastatic diseases at presentation and those who underwent curative resection were excluded. Patient electronic medical records were reviewed to collect baseline data including age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), biliary decompression method, tumor location, tumor diameter (mm), nodal status, pre-treatment carbohydrate antigen 19-9 (CA 19-9) levels. Our Institutional review board approved this study (IRB 101-4715B).

Treatment course. Referral for CRT was done at the discretion of the attending physicians.

Patients in the CRT group received daily fractions of 180 cGy to a total dose of 5,040 cGy in 28 fractions using a three-dimensional conformal radiation planning technique with a linear accelerator of 6MV energy. Concurrent CT given during radiotherapy was gemcitabine 400 mg/m^2 per week. Induction CT followed by CRT was allowed. During induction CT, gemcitabine-based CT was used in nearly all patients (96%). Maintenance CT with gemcitabine after CRT was indicated for patients with non-progressive disease. Patients in the CT alone group received gemcitabine monotherapy or gemcitabine-based combination CT. Gemcitabine was generally given as 1000 mg/m^2 over 30 minutes on day 1, 8 and 15, and was repeatedly every 4 weeks as one course. The CT dose was adjusted at the discretion of the treating physician. At progression, further systemic CT as individual treatment was indicated.

Efficacy and toxicity assessment. Contrast-enhanced computed tomography scan was performed before starting treatment, at the end of CRT or primary CT and then every 3 months during follow-up time. Failure pattern were defined by the first progression event based on radiographic imaging and categorized as locoregional *versus* distant failure. Progression-free survival (PFS) was calculated from the date of diagnosis to date of disease progression, date of death or date of last follow-up. Overall survival (OS) was calculated from the date of diagnosis to date of death or last follow-up. Toxicities were recorded at each visit using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The highest grades of toxicity during primary treatment were recorded.

Statistical analysis. Descriptive statistics were used to characterize patients' characteristics, stratified by receipt of CRT. The Chi-square test or Fisher's exact test was used to compare categorical variables. Non-parametric k-sample test was used to compare median values of continuous variables. Survival analysis between groups was estimated using the Kaplan-Meier method and compared using the log-rank test. All of the tests of hypotheses were 2-sided and *p*-values ≤0.05 were considered statistically significant. Statistical analysis was performed using the SPSS Statistics version 21.0 (link or supplier). The Cox proportion hazards multivariate analysis was used to analyze factors associated with OS.

Results

Patients' characteristics. Fifty-five patients with LAPC received primary treatment in our Hospital. Twenty-six (47%) were male with a median age of 63 years (range, 41-85). Of the 55 patients, 31 patients (56%) received CRT (CRT +CT group) and 24 (44%) received CT alone (CT alone group). The patients' characteristics of both groups were summarized in Table I. The CRT+CT group and CT alone group were similar in terms of age, gender, ECOG PS, pre-treatment CA19-9 levels, tumor size and location. More patients in the CT-alone group than CRT+CT group had lymph node involvement (71% *vs*. 39%, p=0.02), which was the only significant difference in baseline characteristics.

Treatment characteristics. Out of 31 patients in the CRT+CT group, 22 (71%) received induction CT followed by CRT. Half of patients received at least 4 cycles of induction CT with gemcitabine-based regimen (96%). Median dose of radiotherapy and gemcitabine was 50.4 Gy and 2,000 mg/m^2, respectively. The remaining 9 patients received upfront CRT with a lower median dose of 45.6 Gy than those who received induction CT followed by CRT (Table II).

Toxicity and outcome. The toxicity data are summarized in Table III. In both groups, grade 1 or 2 toxicities were common. Patients in the CRT+CT group developed more grade 3/4 gastrointestinal and dermatologic toxicities than those in the CT-alone group. Patients in the CRT+CT group had a median PFS of 8.7 months (95% confidence interval (CI), 7.2-10.3 months) compared to 4.9 months (95%CI=2.9-6.9 months) for patients in the CT alone group (Figure 1). The median OS for CRT+CT group was 14.6 months (95%CI=11.9-17.4 months) and 8.8 months (95%CI=3.7-12.4 months) for the CT-alone group (Figure 2). The pattern of disease progression is documented in Table IV. The sites of first failure in the CRT+CT group included distant metastases in 10 patients (38%), locoregional progression in 10 patients (38%), while 6 patients (23%) had both locoregional progression and distant metastases. In the CT-alone group, 6 patients (27%) had distant metastases.

Prognostic factors. On the univariate analysis of overall survival, CA 19-9 <800 U/ml, responders and receipt of CRT were prognostic factors for better survival (Table V).

Table I. *Patients' characteristics.*

	CRT+CT (n=31)	CT alone (n=24)	*p*-Value
Age at diagnosis, years			0.53[a]
Median	62.0	65.5	
Range	42-83	41-85	
Gender, No. (%)			
Male	14 (45.2)	12 (50)	0.79**
Female	17 (54.8)	12 (50)	
ECOG PS at diagnosis, No. (%)			0.24*
0	8 (25.8)	2 (8.3)	
1	21 (67.7)	20 (83.3)	
2	2 (6.5)	2 (8.3)	
CA19-9, U/ml			0.35[a]
Median	136	317	
Range	1-7556	1-8845	
Biliary decompression at diagnosis, No. (%)			0.53*
None	17 (54.8)	14 (58.3)	
Stent	11 (35.5)	6 (25)	
PTCD	3 (9.7)	2 (8.3)	
Stent and PTCD	0	1 (4.2)	
Hepatoenterostomy	0	1 (4.2)	
Tumor location, No. (%)			0.53*
Head	19 (61.3)	17 (70.8)	
Body/tail	12 (38.7)	7 (29.2)	
Tumor size, mm			0.15[a]
Median	33	39.5	
Range	13-85	20-90	
Unresectability criteria, No. (%)			0.38*
Encasement of celiac trunk	7 (22.6)	5 (20.8)	
Encasement of SMA	14 (58.3)	14 (45.1)	
Encasement of splenoportal trunk	7 (22.6)	4 (16.8)	
Encasement of SMV	2 (6.5)	0	
Unconstructable encasement of IVC	1 (3.3)	0	
Lymph node stage, No. (%)			0.02**
N0	19 (61.3)	7 (29.2)	
N1	12 (38.7)	17 (70.8)	

*Chi-Square test; **Fisher exact test; [a]k-sample test; PS, performance status; PTCD, percutaneous transhepatic cholangial drainage; IVC, inferior *vena cava*; SMV, superior mesenteric vein; SMA, superior mesenteric artery.

Table II. *Treatment characteristics of chemotherapy and radiotherapy (N=55).*

C-CRT, N=22 (%)	
Induction chemotherapy	
Gemcitabine	3 (12.3)
Gemcitabine and Cisplatin	12(50)
Gemcitabine, Oxaliplatin, 5-fluorouracil and leucovorin	6(25)
S1	1(4)
RT dose delivered, cGy	
Median	5040
Range	2200-5040
Receiving <50.4 Gy, No. (%)	7 (29%)
Gemcitabine during concurrent chemoradiotherapy	
Median cumulative dose, mg/m^2	2000
Range, mg/m^2	400-3200
CRT, N=9 (%)	
RT dose delivered, cGy	
Median	4560
Range	2520-5160
Receiving <50.4 Gy, No. (%)	5 (56%)
Concurrent chemotherapy during chemoradiotherapy, No. (%)	
Gemcitabine	8 (89)
5-fluorouracil	1 (11)
Median cumulative dose of gemcitabine, mg/m^2	2000
Range, mg/m^2	400-3200
CT alone, N=24 (%)	
Gemcitabine and Cisplatin	7 (29)
Gemcitabine	13 (54)
Gemcitabine -nanoplatin	2 (8)
Gemcitabine and S1	1 (4)
GOFL then gemcitabine alone	1 (4)
Cumulative dose of gemcitabine, mg/m^2	
Median	6500
Range	1000-24000

C-CRT, induction chemotherapy followed by concurrent chemoradiotherapy; CRT, concurrent chemoradiotherapy; CT, chemotherapy; GOFL, gemcitabine, oxaliplatin, 5-fluorouracil and leucovorin; RT, radiotherapy; Gy, gray; mg, milligram.

Multivariate analysis showed that responders (adjusted HR, 0.24; 95% CI, 0.12-0.56) and receipt of CRT (adjusted HR, 0.35; 95% CI, 0.18-0.67) were independently associated with increased OS.

Discussion

In the present study, we observed a prolonged median survival of 14.6 months in the CRT+CT group. The result was comparable to the historical median overall survival time (11.9-15.3 months) reported in the studies of induction CT following concurrent CRT (4, 6, 18-20). The frequency of grade 3-4 toxicity in the CRT+CT group was higher than the CT-alone group while most treatment related toxicities were manageable. There was no treatment-related mortality. These findings suggest that the anti-tumor activity of CRT confers a survival benefit and the toxicity profile is acceptable.

There is no consensus whether CT-alone or primary CRT is to be considered the standard-of-care. The FFCD study randomly assigned patients to either CRT followed by maintenance gemcitabine, or gemcitabine alone until progression. The CRT arm consisted of radiation delivered to 60 Gy in 2Gy/ fraction with an infusion of 5-FU (300 mg/m^2 over 24 h five days per week) and cisplatin (20 mg/m^2/day) on days 1 to 5 during weeks 1 and 5. The study was halted because of slow accrual, while the survival analysis showed a

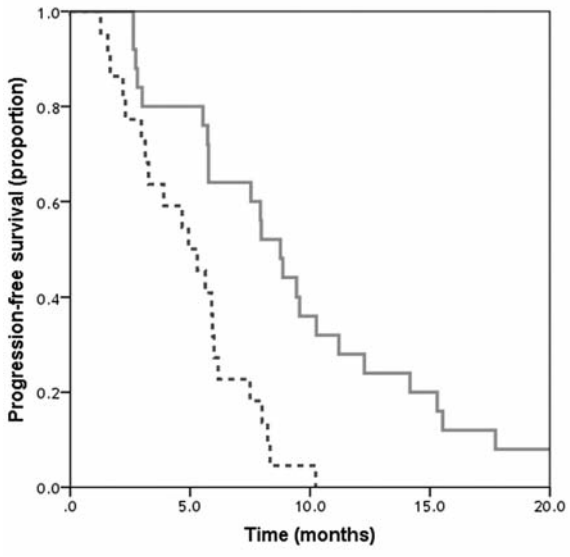

Figure 1. *Progression-free survival among patients with locally advanced pancreatic cancer is shown according to receipt of chemoradiotherapy. CRT+CT, chemoradiotherapy with chemotherapy; CT alone, chemotherapy alone.*

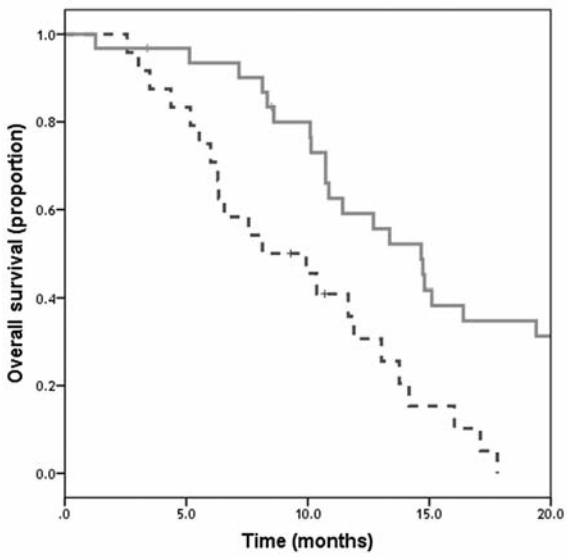

Figure 2. *Overall survival among patients with locally advanced pancreatic cancer is shown according to receipt of chemoradiotherapy. CRT+CT, chemoradiotherapy with chemotherapy; CT alone, chemotherapy alone.*

Table III. *Toxicity in patients treated with chemoradiotherapy and chemotherapy alone (N=55).*

Toxicity	CRT+CT (N=31)		CT alone (N=22)	
Hematologic	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Leukopenia	21 (67%)	5 (12.5%)	18 (82%)	0
Neutropenia	20 (62.5%)	6 (17%)	14 (64%)	2 (9%)
Lymphopenia	20 (58.3%)	2 (4.1%)	8 (36%)	0
Anemia	25 (75%)	2 (8.2%)	14 (64%)	0
Thrombocytopenia	15 (46%)	4 (16.4%)	6 (27.2%)	2 (9%)
Non-Hematologic	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Nausea	21 (58%)	2 (8.2%)	11 (50%)	0
Vomiting	16 (45%)	2 (4.1%)	8 (36.4%)	0
Diarrhea	7 (20.5%)	2 (4.1%)	4 (18.1%)	0
GI Bleeding	2 (4.1%)	0	1 (4%)	0
Elevated AST/ALT	8 (29.2%)	0	10 (45.5%)	

CRT+CT, patients received concurrent chemoradiotherapy; CT, patients received chemotherapy alone; GI, gastrointestinal; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table IV. *Failure pattern (N=48)*.*

No. (%)	CRT+CT	CT alone
Locoregional progression	10 (38.4)	6 (27.3)
Metastases only	10 (38.4)	6 (27.3)
Both	6 (23.2)	10 (45.4)

*7 patients have no data of follow-up CT scan to assess disease progression; these patients also were censored in the analysis of time to progression survival. CRT+CT, patients received concurrent chemoradiotherapy; CT, patients received chemotherapy alone.

better median survival with gemcitabine alone (13 months) compared to chemoradiation (8.6 months) by intent-to –treat analysis (p=0.03). The interpretation of the results was limited by the non-standard design with higher radiation dose (60 Gy) and concurrent CT with cisplatin, which may compromise tolerability of the CRT arm. The ECOG 4201 study directly compared gemcitabine alone with gemcitabine-based CRT (50.4 Gy in 28 fractions and concurrent gemcitabine 600 mg/m^2 weekly) followed by gemcitabine. The study was prematurely terminated because of poor accrual and only 74 patients enrolled for analysis. However, this study using a modern CRT showed a slight improved survival in favor of CRT (11.1 *vs*. 9.2 months) (15). The results of the two studies were contradictory. These findings suggest that the feasibility of CRT and toxicity management is critical to improve the treatment efficacy. In our study, the majority of patients received gemcitabine-based (400 mg/m^2/week) during the radiotherapy course. Of the 31 patients in the CRT+CT group, 23 (77%) received at least 45 Gy. The RT compliance and toxicities were similar to previous studies of gemcitabine-based CRT (15, 21, 22).

Table V. *Prognostic factors of overall survival on univariate and multivariate analysis.*

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (≥65 *vs*. <65 years)	0.86 (0.48-1.53)	0.61		
CA 19-9 at diagnosis (≥800 *vs*. <800 U/ml)	2.01 (1.04-3.85)	0.03	1.41 (0.68-2.9)	0.35
Tumor size (≥3 *vs*. <3 cm)	1.54 (0.81-2.94)	0.18		
Performance status (≥2 *vs*. <2)	1.01 (0.36-2.83)	0.98		
Treatment modality (CRT *vs*. CT alone)	0.36 (0.19-0.67)	<0.01	0.35 (0.18-0.67)	0.002
Overall response (non-PD *vs*. PD)	0.22 (0.11-0.45)	<0.01	0.24 (0.11-0.46)	0.001

HR, Hazard ratio; CI, confidence interval; PD, disease progression.

Treatment of LAPC continued to evolve in hopes of achieving better survival. A new strategy of administering CRT after initial CT in patients with no evidence of disease progression has been investigated in several retrospective series (4, 16, 17). These studies indicate that CRT following induction CT may be more active than continuing CT alone or primary CRT. However, this approach is not supported by the LAP 07 study. The international phase III study compared CRT to CT in LAPC-controlled after 4 months of induction CT. Patients in the CRT group received 54 Gy radiotherapy plus concurrent capecitabine 1,600 mg/m^2 per day. In a preliminary report presented at the 2013 American Society of Clinical Oncology (ASCO) annual meeting (23), no significant difference was observed in median overall survival between the CT arm and CRT arm (16.4 months *vs*. 15.2 months, p=0.8295). RT compliance may be one of the issues. Only 32 percent of patients in the CRT arm were treated per protocol. Interpretation of these data requires more analysis after publication of the final results.

Sequential treatment after primary CRT or CT alone might have an impact on survival (24-26). Many studies of CRT-administered maintenance CT with gemcitabine after the completion of CRT (8, 14, 15, 27-29). In our study, 18 (58%) patients of the CRT+CT group received post-CRT CT with gemcitabine. These patients who ever received post-CRT CT had significantly better survival than those who did not receive subsequent CT, with median times of 20.9 and 10.1 months, respectively (p=0.001). The issue of maintenance CT should be addressed by further prospective studies. In contrast, there is no consensus on the indication for salvage CRT after failure of primary CT. A retrospective study enrolled 30 patients who received primary CT until progression or unacceptable toxicity (30). The failure pattern of all patients was locoregional progression but not distant metastases. These patients underwent salvage CRT combined to either S-1 or 5-FU. The median survival time from the start of salvage CRT and the start of primary CT was 8.8 months and 17.8 months, respectively. The strategy of administering salvage CRT following primary CT should be investigated in prospective trials.

Multivariate analysis revealed that tumor response is a predictor for better survival. Our results showed that patients with disease progression as the best response had shorter OS than those with stable disease or tumors responding to treatment. The finding concurs with the results of a retrospective study, which showed that OS was longer in the responding group compared with the non-responding group (15.8 *vs*. 7.5 months, respectively) (21).

Given the retrospective nature of the present study, the reasons for choosing treatment strategy are at the physician's discretion. Other unmeasured selection bias may inevitably exist. However, patients are consecutively collected during a period of 7 years. The clinicopathological characteristics were balanced between the CRT+CT group and the CT-alone group except for nodal status. The bias is most likely equal across both two groups. Secondly, the information regarding subjective toxicities abstracted from retrospective data is inherently incomplete. We recorded nausea/vomiting and diarrhea as toxicities of interest according to, not only patient records but also, the prescribed medications.

In conclusion, this study demonstrated the survival benefit of administering CRT combined with either induction or subsequent CT for patients with LAPC. The feasibility and tolerability of CRT is critical for patients to complete the treatment course and achieve potential efficacy. Radiotherapy up to 50.4 Gy combined with gemcitabine 400 mg/m^2 per week is tolerable. Further prospective studies are warranted to compare CT alone with gemcitabine with gemcitabine-based CRT for patients with LAPC.

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