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Outcome Analysis of Chemoradiation in Unresectable Pancreatic Cancer Focusing on Treatment Sequencing Strategy

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Abstract. *Aim: To analyze the outcomes of patients with unresectable pancreatic cancer after chemoradiotherapy (CCRT), focusing on sequencing strategy. Patients and Methods: Data of 144 patients treated from January 1989 to December 2013 were retrospectively analyzed. Patients were divided into the scheduled group (N=27), salvage group (N=37) and upfront group (N=80) per CCRT and chemotherapy sequence. Results: With a median follow-up of 10.4 months (range=1.4-164.2), median overall survival (OS) was 13.5 months. Patients in the upfront group had inferior performance status and received a lower radiation dose (p=0.007 and p<0.001, respectively). Higher radiation dose (≥45 Gy) was the sole prognosticator related with improved survival in multivariate (p=0.001) analysis, whereas treatment sequence was not a significant prognostic factor (p=0.409). Conclusion: No difference was found among tested sequencing strategies that were all well-tolerated, despite skewed distribution for performance and radiation dose. An upfront approach may be a viable option for patients with limited performance to undergo more active systemic chemotherapy.*

It is well known that the prognosis of pancreatic cancer is dismal. Reported overall survival (OS) of patients with pancreatic cancer is only around 5% at 5 years (1, 2). Even though surgical resection remains the only curative treatment, only 20-25% of patients at the time of diagnosis are considered as candidates for surgery. Of remaining patients, about 30% are presented with locally advanced lesion without distant metastasis (3, 4).

Although chemotherapy plays pivotal role, concurrent chemoradiotherapy (CCRT) has also been employed based on reported survival benefit over radiotherapy (RT) alone or chemotherapy alone (5-9). Chemotherapies are often applied before CCRT both to control systemic disease upfront and to select proper candidates for CCRT (10). However, optimal sequencing strategies have not been elucidated. The aim of the study was to analyze the results of CCRT for patients with unresectable pancreatic cancer focusing on sequencing strategy.

Patients and Methods

After Institutional Review Board (IRB) approval, medical records of 178 consecutive patients with unresectable pancreatic cancer without distant metastasis, who underwent CCRT from January 1989 to December 2013, were reviewed. Twenty-seven patients were initially excluded as palliative surgery was offered prior to CCRT, while one patient was excluded due to incomplete medical record. Six patients were further excluded after intensive medical record and image review as lesions were deemed resectable by current standards. Unresectability was defined as lesions invading or encasing major arteries, such as superior mesenteric artery, celiac axis and hepatic artery and/or long segment invasion and encasement of major veins, such as superior mesenteric vein and portal vein, not amendable to reconstruction after review by panel of radiologists and surgeons. Therefore, a total of 144 patients were analyzed in the present study. Patients were retrospectively divided into three groups for comparison. Chemotherapy followed by scheduled CCRT, the scheduled group (N=27). Chemotherapy followed by initially unplanned CCRT, the salvage group (N=37). Lastly, CCRT offered as initial treatment, which may be followed by further chemotherapy, the upfront group (N=80).

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Key Words: Pancreatic cancer, chemoradiotherapy, chemotherapy, radiation dose.

Table I. *Patients' characteristics*.

Characteristic	N (%)				*p*-Value
	All	Scheduled	Salvage	Upfront	
Age (years)					
Median	59.8	56.8	61.4	61.0	0.109*
Range	32.6-78.4	35.7-72.7	46.0-77.3	32.6-78.4	
Gender					
Female	62 (43.1)	11 (40.7)	20 (54.1)	31 (38.8)	0.288†
Male	82 (56.9)	16 (59.3)	17 (45.9)	49 (61.3)	
Performance (ECOG)					
0-1	122 (84.7)	26 (96.3)	35 (94.6)	61 (76.3)	0.007†
2-3	22 (15.3)	1 (3.7)	2 (5.4)	19 (23.8)	
Tumor location					
Head	71 (49.3)	9 (33.3)	15 (40.5)	47 (58.8)	0.034†
Body or tail	73 (50.7)	18 (66.7)	22 (59.5)	33 (41.3)	
Lymph node involvement					
No	85 (59.0)	17 (63.0)	17 (45.9)	51 (63.8)	0.171†
Yes	59 (41.0)	10 (37.0)	20 (54.1)	29 (36.3)	
Radiation dose (Gy)					
Median	50.4	55.8	54.0	40.0	<0.001*
Range	40.0-59.4	50.4-55.8	40.0-59.4	40.0-56.0	

ECOG, Eastern Cooperative Oncology Group. *One-way ANOVA test; †Chi-square test.

RT target volume contained primary tumor plus margin for microscopic disease extension and grossly enlarged lymph nodes, as well as elective regional nodal area. Dose over 45 Gy was confined to primary tumor and grossly enlarged lymph nodes.

All adverse events were evaluated using Common Terminology Criteria for Adverse Events version 4.0. Each event was scored regardless of the other and the highest grades of complications observed during CCRT were recorded. Late gastrointestinal toxicities related to RT were graded separately.

Comparisons of selected characteristics between patients among three groups were carried out using the Pearson's Chi-square test for categorical variables and the one-way ANOVA test for continuous variables. OS was counted from the first date of any kind of treatment to the date of death and calculated by the Kaplan-Meier method. Post-RT survival was defined as the duration between the last date of RT and the date of death. Log-rank test was performed for the comparison of OS depending on categorical variables. The backward Cox regression model was used for multivariate analysis and analysis of the effects of continuous variables on OS. Prognostic factors with $p<0.1$ in the univariate analysis were incorporated in multivariate analysis. Maxstat, a maximal Chi-square method in R2.13.0 (R Development Core Team, Vienna, Austria, http://www.R-project.org) was used to define the optimal cut-off radiation dose to show maximal difference of OS. Statistical significance was defined as $p<0.05$ in a two-sided test. Data were analyzed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patients' characteristics. Median age at the start of the treatment was 59.8 years old (range=32.6-78.4). Patients' distribution was skewed for performance, lesion location and radiation dose. More patients in the upfront group had limited performance defined as Eastern Cooperative Oncology Group performance scale 2 or higher ($p=0.007$). Head lesions were also more frequent in the upfront group ($p=0.034$). Median radiation dose was statistically different among groups with 55.8 Gy (range=50.4-55.8), 54.0 Gy (range=40.0-59.4) and 40.0 Gy (range=40.0-56.0) for the scheduled group, the salvage group and the upfront group, respectively ($p<0.001$). Other characteristics, including age, gender and frequency of lymph node involvement, were comparable among three groups (Table I).

Treatment. In the scheduled group, gemcitabine-based chemotherapy regimens were the mainstay of treatment. Combination with cisplatin was most frequently used with 2 cycles for one patient, 3 cycles for 18 patients and 4 cycles for the other patient. Other platinum combination regimens include two patients with 3 cycles with oxaliplatin and one patient with 2 cycles with carboplatin. Erlotinib combination was offered to two patients for 7 cycles and 4 cycles, respectively. Remaining two patients were treated with 2 cycles of gemcitabine and capecitabine. Response after scheduled chemotherapy was partial response for 4 patients and stable disease for 23 patients using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST). Employed chemotherapies during RT were capecitabine for 22 patients, two cycles of 5-fluorouracil (5-FU) for 2 patients and weekly gemcitabine for 3 patients.

Gemcitabine-based chemotherapy was also most commonly used regimen in the salvage group. This included 2 cycles (N=4), 3 cycles (N=4), 4 cycles (N=1), 5 cycles (N=1), 6 cycles (N=3), 9 cycles (N=3) and 12 cycles (N=1) of gemcitabine plus erlotinib (N=17), 2 cycles (N=2), 3 cycles (N=1), 4 cycles (N=3) and 6 cycles (N=1) of gemcitabine plus cisplatin (N=7), one cycle (N=1), 2 cycles (N=1), 3 cycles (N=1) and 4 cycles (N=2) of gemcitabine alone (N=5), 3 cycles (N=1) and 4 cycles (N=1) of gemcitabine, oxaliplatin and erlotinib (N=2), 15 cycles of gemcitabine and capecitabine (N=1) and 7 cycles of gemcitabine and caboplatin (N=1). Three patients were initially treated with gemcitabine chemotherapy then had regimen changed to fluoropyrimidine-based chemotherapy; 5 cycles of gemcitabine followed by 2 cycles of capecitabine (N=1), 6 cycles of gemcitabine then 2 cycles of 5-FU (N=1) and 6 cycles of gemcitabine followed by 18 cycles of 5-FU (N=1). There was one patient undergoing 3 cycles of FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) prior to CCRT. Tumor responses by RECIST criteria were partial response in 4 patients, stable disease in 23 patients and progressive disease in 10 patients. During CCRT, 14 patients received weekly gemcitabine, 12 patients were treated with capecitabine, 7 patients were treated with 5-FU on Days 1-3 and Days 29-31, while three patients received 5-FU on Days 1-3. One patient received 2 cycles of gemcitabine.

In the upfront group, 56 patients received two cycles of 5-FU, 8 patients underwent one cycle of 5-FU, 13 patients weekly gemcitabine and 3 patients daily capecitabine.

Median radiation dose were 55.8 Gy (range=50.4-55.8), 54.0 Gy (range=40.0-59.4) and 40.0 Gy (range=40.0-56.0) for the scheduled group, salvage group and upfront group, respectively.

Various regimens of chemotherapy following CCRT were offered to patients with suitable performance. Chemotherapy was given to 20 patients (74.1%) in the scheduled group, 24 patients (64.9%) in the salvage group and 31 patients (38.8%) in the upfront group.

Overall survival. With the median follow-up duration of 10.4 months (range=1.4-164.2), the median OS was 13.5 months (95% confidence interval (CI)=11.49-15.51), 16.3 months (95% CI=14.43-18.17), 17.5 months (95% CI=14.93–20.07) and 10.1 months (95% CI=8.74-11.46) for all patients, scheduled group, salvage group and upfront group, respectively (Figure 1, p=0.007). Accordingly, post-RT median OS was 9.4 months (95% CI=8.17-10.63), 12.4 months (95% CI=9.18-15.62), 10.8 months (95% CI=7.25-14.35) and 8.8 months (95% CI=7.82-10.63), respectively (p=0.452).

Prognostic factors. Table II provides results of univariate and multivariate analyses of prognostic factors for OS. Maximal

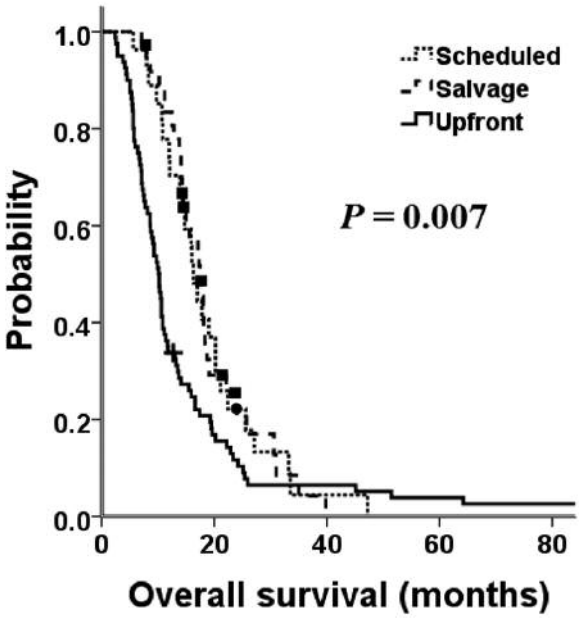

Figure 1. *Kaplan-Meier survival curve per treatment sequence*.

Chi-square test nominated 45 Gy as the optimal cut-off value for OS-related radiation dose (Figure 2, p=0.038). Radiation dose was the only significant factor with both univariate (p=0.001) and multivariate (p=0.001) analyses. In terms of post-RT OS, radiation dose was also a significant factor (p=0.038). Treatment group was analyzed as a significant prognostic factor with univariate analysis for OS (p=0.007), but lost its significance after multivariate analysis (p=0.409). Other factors, such as age, gender, ECOG performance status, tumor location, lymph node involvement and carbohydrate antigen (CA) 19-9, were not deemed significant.

Adverse events. Details of recorded acute and late adverse events are as described in Table III. Most common grade 1-2 toxicity was nausea or vomiting in all three groups. There was no complication requiring surgical intervention.

Discussion

In this retrospective review of 144 patients treated with CCRT for unresectable pancreatic cancer, the median OS was 13.5 months. We showed that radiation dose was the only significant prognosticator in both univariate and multivariate analyses. Treatment sequence affected OS significantly with univariate analysis, but lost its significance after multivariate analysis, whereas post-RT OS was not significantly different across the groups. This could be due to selection bias or radiation dose effect on the scheduled and salvage group against the upfront group.

Table II. *Prognostic factor analysis*.

	N	OS	*p*-Value		Post-RT OS	*p*-Value	
		(median, months)	UVA*	MVA†	(median, months)	UVA*	MVA†
Age							
<70 years	119	13.8	0.903	–	9.4	0.868	–
≥70 years	25	13.2			9.6		
Gender							
Female	62	14.1	0.832	–	10.2	0.884	–
Male	82	11.2			9.3		
Performance (ECOG)							
0-1	122	14.2	0.208	–	10.0	0.419	–
2-3	22	9.3			5.6		
Tumor location							
Head	71	11.2	0.794	–	8.5	0.770	–
Body or tail	73	13.8			10.4		
Lymph node involvement							
No	85	12.8	0.626	–	9.4	0.914	–
Yes	59	14.1			9.7		
Initial CA 19-9 level‡							
<1000 U/ml	71	15.6	0.581	–	10.8	0.591	–
≥1000 U/ml	33	14.2			9.9		
Post-RT CA 19-9 level‡							
<37 U/ml	33	17.8	0.126	–	12.4	0.409	–
≥37 U/ml	64	14.3			10.8		
Radiation dose							
≤45 Gy	57	9.3	0.001	0.001	7.7	0.038	0.039
>45 Gy	87	16.0			12.2		
Treatment group							
Scheduled	27	16.3	0.007	0.409	12.4	0.452	–
Salvage	37	17.5			10.8		
Upfront	80	10.1			8.8		

OS, Overall survival; mo, months; UVA, univariate analysis; MVA, multivariate analysis; ECOG, Eastern Cooperative Oncology Group; CA 19-9, carbohydrate antigen 19-9. *Log-rank test; †Cox regression analysis. ‡Patients with missing value excluded from the analysis.

There is an on-going debate on optimal treatment for unresectable pancreatic cancer. Various combinations of RT, chemotherapy and CCRT have been employed in practice and studied. However, best treatment sequence, duration, dose and regimen have yet to be established as reflected in studies reported over period of time from GITSG, FFCD/SFRO, GERCOR and LAP (5, 6, 8, 11-13).

Many researchers have contributed in search of the optimal chemotherapy regimen for unresectable pancreatic cancer, as well. Most recent studies have shown improved results with more active FOLFIRINOX regimen over gemcitabine and more traditionally used fluoropyrimidine-based chemotherapy (14, 15). However, this was accompanied by significant toxicities. Combining gemcitabine with nanoparticle albumin-bound (nab)-paclitaxel was shown to have similar efficacy with less toxicity (16). In the current study, the majority of employed chemotherapy regimens was gemcitabine-based, except for one patient undergoing FOLFIRINOX regimen and none treated with combination nab-paclitaxel. This is, at least in part, owing to period of patient accrual for analysis, when results of aforementioned studies were unavailable.

For CCRT, Li *et al*. (17) reported improved OS in gemcitabine-treated group compared to 5-FU-treated group (p=0.027). In randomized phase II trial, Mukherjee *et al*. (18) suggested capecitabine-based CCRT might be better than gemcitabine-based CCRT after induction chemotherapy (p=0.012). In the current study, patients were treated with 5-FU, gemcitabine and capecitabine reflecting transition of the mainstay of combined chemotherapy with RT over accrued time period.

Treatment sequencing strategy employing both chemotherapy and CCRT has long been an issue, when CCRT was incorporated as a component of a treatment. With advance in chemotherapy, treatment sequence has been shifted from upfront CCRT followed by chemotherapy, as in early GITSG studies to chemotherapy followed by CCRT, as in a more recent LAP07 study. The latter approach has been favored

Table III. *Complications graded by CTCAE 4.0.*

	Number of patients (%*)					
	Grade 1-2			Grade 3-4		
	Scheduled	Salvage	Upfront	Scheduled	Salvage	Upfront
Hematological toxicity						
Leukopenia	4 (14.8)	12 (32.4)	20 (25.0)	1 (3.7)	4 (10.8)	3 (3.8)
Neutropenia	2 (7.4)	7 (18.9)	5 (6.3)	0 (0.0)	1 (2.7)	3 (3.8)
Anemia	5 (18.5)	5 (13.5)	8 (10.0)	0 (0.0)	2 (5.4)	0 (0.0)
Thrombocytopenia	5 (18.5)	1 (2.7)	5 (6.3)	0 (0.0)	1 (2.7)	1 (1.3)
Nausea/Vomiting	13 (48.1)	6 (16.2)	37 (46.3)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	0 (0.0)	1 (2.7)	2 (2.5)	1 (3.7)	0 (0.0)	0 (0.0)
Diarrhea	3 (11.1)	1 (2.7)	5 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Enteritis	5 (18.5)	3 (8.1)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Skin rash	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Dizziness	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hand foot syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)
Late GI toxicity	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (1.3)

CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal. *Percentage of each subgroup (scheduled group=27 patients, salvage group=37 patients and upfront group=80 patients, respectively).

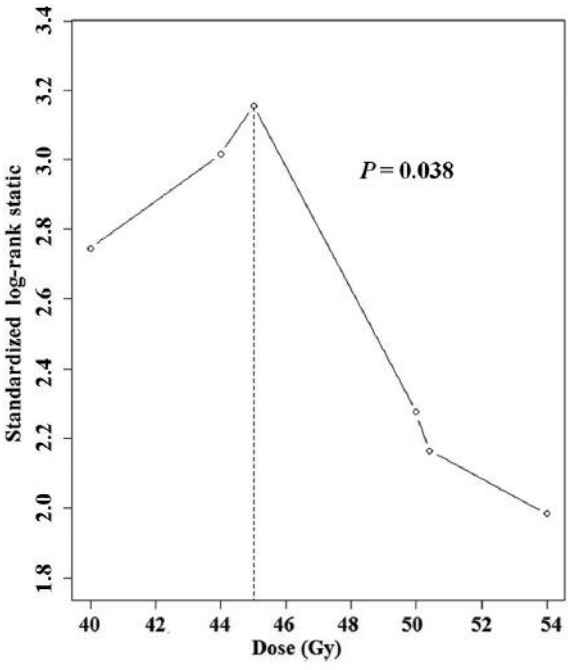

Figure 2. *Maximal Chi-square method: the cut-off value of radiation dose was set to what provided the best separation of OS into two groups, where the standardized log-rank statistics take their maximum.*

recently based on two major factors; First, full dose delivery of active chemotherapy for fit patients and, second, possible selection for patients more suitable to benefit from additional locoregional modality. Some of the best treatment results are reported from more recent phase II studies employing induction chemotherapy followed by CCRT (19, 20). Patients accrued in the current study followed this trend with more patients treated with upfront approach followed by salvage approach and then, more recently, with scheduled sequencing.

As shown in results, survival was significantly different for treated group on univariate analysis. However, treatment group lost its statistical significance after correcting for skewed distribution of radiation dose, that was the sole significant prognosticator, through multivariate analysis. Of note is that, unlike in prospective trials, patient selection is inherently biased. In this case, patients without distant metastasis after initial chemotherapy, either as scheduled or salvage, were selected to undergo CCRT. On the contrary, in the upfront group, as it was the initial treatment offered, all patients were included. Thus, patient selection would have been biased against upfront group. Furthermore, there was no difference in post-RT survival irrespective of treatment group. This might have stemmed from the limited number of patients, as there was clearly numerical difference across the treatment strategy. Thus, these results may provide a rationale in favor of either scheduled or salvage approach. However, considering selection bias against upfront CCRT and skewed distribution of patients with poor performance, this could also be interpreted as a safe and effective application of CCRT not only for those not deemed suitable for systemic chemotherapy, especially more active and potent treatment with increased toxicity, but also for general

application as well. Incorporating CCRT as a component of treatment resulted in improved survival in comparison to chemotherapy alone within the same institution (21). Thus, CCRT, as a component of treatment for patients with unresectable/non-metastatic pancreatic cancer, needs to be further tested. Optimal timing of CCRT, in addition to other aspects of treatment, including optimal regimen, may be a subject for further studies.

It has also been a separate question to define an optimal radiation dose in regards to both efficacy and safety for CCRT in unresectable pancreatic cancer. Dose escalation has been attempted cautiously due to increased risk of detrimental toxicities. Best example maybe previously mentioned FFCD/SFRO study, where patients treated to high-dose radiation with active chemotherapy regimen resulted in inferior survival (12). Similarly, in a retrospective study based on national cancer data base, Hall *et al*. examined radiation dose escalation above 40 Gy in CCRT but failed to validate the benefit in terms of OS (22). However, more than 54 Gy of radiation dose was associated with better OS in a more recent retrospective study by Golden *et al*. (23). Factor to be considered here is relevant expertise in the patient care. It is well known that expertise in surgical resection, reflected as hospital load or surgical volume, plays significant role, more so in pancreatic cancer than any other malignancies (24). For radiotherapy, this may be termed as importance of quality assurance, which has been highlighted through a multi-center prospective randomized study conducted by Radiation Therapy Oncology Group (RTOG), where adherence to the protocol resulted in not only significantly improved survival but also significantly decreased toxicity (25). In the present study, higher radiation dose (≥45 Gy) showed improved OS in both univariate and multivariate analyses, sustaining significance as a continuous variable as well. Further analysis awaits to confirm radiation dose effect on OS in patients with unresectable pancreatic cancer treated with modern advanced radiation technique adhering to target volume and normal tissue delineation guidelines.

Our study has several limitations. First, given its retrospective nature, the potential for selection bias cannot be excluded as discussed previously. Second, patients were accrued in a time period of over 25 years. This wide range of accrual is somewhat reflected in various chemotherapy regimens employed. Also, CA 19-9 values, known to be important prognostic factor (23, 26), were unavailable for more than one-third of the patients, especially those treated in earlier period, which may have impacted current prognosticator analysis.

In conclusion, CCRT could be a reasonable treatment option for unresectable pancreatic cancer, especially in patients not fit for more active chemotherapy. Results from the current study also add additional evidence in favor of radiation dose escalation. Optimal sequence for chemotherapy and CCRT combination should be given a chance to be evaluated through a prospective randomized controlled trial.

Conflicts of Interest

None.

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