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Adjuvant Chemo-Radiotherapy *versus* Chemotherapy in Pancreatic Carcinoma

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Background: Pancreatic carcinoma has the worst prognosis of all gastrointestinal solid tumors. Only 15-20% of cases present at a resectable stage and the rate of local recurrence is high.
Aim: To assess tolerability and efficacy of adjuvant chemo-radiotherapy (CRT) for pancreatic carcinoma compared to chemotherapy (CTH) alone.
Methods: This was a prospective study with historical control group. The intervention group involved patients who underwent a 3-phases protocol following Whipple surgery. In the first phase, weekly gemcitabine was administered at a dose of 1 gm/m^2 for 3 weeks. The second was a CRT phase whereas capecitabine (800 mg/m^2) used twice daily for 5-6 weeks concurrent with 3 dimensional conformal radiotherapy. Finally, the maintenance phase in which gemcitabine administered at a dose of 1 gm/m^2 weekly for 3 weeks with 1 week rest for 3 cycles. The historical group included patients who received gemcitabine only within the preceding 2 years.
Results: From 50 patients with pancreatic cancer in the intervention group, 41 completed the treatment protocol *versus* 40 patients in the control group. The estimated median disease-free survival was 15 months in the CRT group *versus* 10 months in the CTH group, and the estimated mean was 19.4 versus 13.2 ($p = 0.041$). The estimated median overall survival was not reached in both treatment arms. The estimated mean overall survival was 27.9 months in the CRT group compared to 19.2 months in the CTH group ($p = 0.023$). The relapse rate was 29% in the CRT group versus 65% in the CTH group ($p= 0.001$). CRT was associated with more toxicity which was tolerated with no interruption of treatment.
Conclusions: Adjuvant gemcitabine before and after capecitabine concurrent with 3D conformal radiotherapy was tolerated with better survival and local control in pancreatic cancer patients.

Keywords: Pancreatic carcinoma; Adjuvant treatment; Chemo-radiotherapy; Chemotherapy.

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INTRODUCTION

Pancreatic carcinoma has the worst prognosis of the solid tumors. It is one of the top ten incidence cancer in Europe and USA, with an overall five-year survival rate five % or less [1]. Surgery is the only way for a cure, but only 15-20% of cases present with resectable disease [2]. After surgery, the median survival ranges from 17 to 27 months. This supports the need for a multidisciplinary approach to decrease the incidence of both distant and loco-regional recurrence [3].

Adjuvant treatment with chemotherapy (CTH) or chemoradiotherapy (CRT) showed an improvement of survival when compared to observation [4]. Meta-analyses trials including regimens based on gemcitabine or 5-fluorouracil showed significant improvement in the median overall survival (OS) of about seven months in patients with a negative safety margin (R0), but with less effect in those with a microscopically positive safety margin (R1) [5-7].

The role of adjuvant radiotherapy is still controversial [8-9]. Radiotherapy may be of benefit for R1 resections cases that are at high risk of loco-regional recurrence [9].

This study was conducted to compare the efficacy and tolerability of adjuvant concurrent CRT (intervention group) for resectable pancreatic carcinoma *versus* adjuvant CTH alone (historical control group).

METHODS

This is a prospective study with historical control group. The intervention group included all pancreatic cancer cases underwent Whipple surgery and referred within one month postoperatively to the Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital in the period from February, 2014 to March, 2016. The historical group had patients with the same criteria within the preceding 2 years, from February 2012 to January 2014.

Selection of patients

Inclusion criteria: Resectable nonmetastatic pancreatic cancer which underwent Whipple surgery and histopathology confirmed the diagnosis of pancreatic adenocarcinoma. Other inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, adequate organ function (renal and liver function tests) and bone marrow functions (normal complete blood picture). Written informed consents had been obtained.

Exclusion criteria: Evidence of gross residual, recurrent or metastatic disease, abnormal organ function (double normal levels and more), ECOG performance status of 3-4, and previous administration of systemic chemotherapy or abdominal radiotherapy.

Post-surgical assessment

Hematological and biochemical laboratory evaluation with tumor markers (CEA and CA 19-9) and post-contrast computerized tomography (CT) scan of the abdomen and pelvis one month postoperatively.

Treatment protocol

Intervention group: All patients were planned to undergo the following 3-phases protocol. The 1st phase included gemcitabine (1000 mg/m^2) intravenous (IV) over 30 minutes weekly for 3 weeks (1 cycle). The 2nd phase started 1-2 weeks after gemcitabine and included concurrent CRT with oral capecitabine (800 mg/m^2) twice daily plus radiation for 5-6 weeks during radiation. The 3rd phase started 3-5weeks after CRT and included the administration of gemcitabine (1gm/m^2) IV over 30 minutes on days 1, 8 and 15; to be repeated every 28 days for 3 months.

3D-conformal radiotherapy to the tumor bed and draining lymph nodes was delivered at a dose of 1.8 Gy/fraction with a total dose ranging between 45 Gy for R0 cases and 54 Gy for R1 cases. CT-based treatment planning (with oral and intravenous contrast-enhanced CT scan using 3 mm slices) was required for all patients. All patients were simulated in comfortable, fixed and supine position with arms should be above the head. The growth target volume (GTV) including: in a case with a positive margin (R1) which described in both pathology and operative reports. The clinical treatment volume (CTV) included: proper coverage of the drainage lymph nodes (including the para-aortic nodes), portal vein segment, celiac artery, and superior mesenteric artery, pancreatico-jejunostomy and the postoperative bed. The planning target volume (PTV) was determined by adding 5 mm surrounding the CTV to which a total dose of 45 Gy (1.8 Gy/fraction for 25 fractions) was delivered. The planning target volume boost (PTV2) was planned with an additional 5 mm around GTV to dose of 9 Gy (1.8 Gy/fraction for 5 fractions) for positive safety margin cases.

Planning was done using 3D Precise Treatment Planning System version 2.12. Optimization of 3D-conformal radiotherapy plan was confirmed with cumulative dose volume histogram. CTV was covered by 95% of isodose curves, inhomogeneity ranged from 95% to 105%, and doses to organs at risk were limited to their tolerances. 3D-conformal radiotherapy was delivered by the high energy linear accelerator (Elekta, Precise Treatment System TM), Version 5, with 6 or 15MEV photon energy.

Historical control group: All pancreatic cancer patients who met the inclusion criteria within the previous two years were included. These patients received gemcitabine 1 gm/m^2 IV in about 30 min every week for 7 weeks then 1 week off treatment then gemcitabine 1 gm/m^2 IV in half an hour on days 1, 8 and 15; to be repeated every 28 days for 4 months.

Evaluation and follow-up

During treatment, all patients were evaluated weekly clinically and toxicities were recorded. Post-treatment evaluation was done at least 1 month after the end of treatment protocol using post contrast (CT or MRI) abdomen and pelvis and tumor markers (CA19-9 and CEA). Patients were followed up every month by clinical examination, a complete laboratory investigations, tumor markers and evaluation of toxic effects, every 3 months by (CT or MRI) for 1 year then every 6 months for the second year then annually.

Treatment-related toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.

Statistical analysis

Disease-free survival (DFS) and Overall survival (OS) were calculated with using The Kaplan–Meier product limit method. Statistical analyses were performed using (SPSS-version 22). Cox regression was used to analyze factors related to survival in order to determine predictors that might have a significant effect on survival.

RESULTS

A total of 50 patients with pancreatic cancer who underwent Whipple surgery were enrolled in the intervention group. Forty-one patients completed the treatment protocol in the intervention group as 2 patients lost to follow-up during the first phase of the treatment protocol and 7 patients developed metastases so they were excluded from the study. The historical control group included 40 patients.

The characteristics of 41 patients enrolled in the CRT group *versus* 40 patients in CTH group are summarized in Table 1. The average age of patients was 55 years (±7.8) in the intervention group and 54.8 years (±8.1).

There was no statistical significant difference between both groups except for tumor size (T) with a p value of 0.03.

This study was done to assess survival significance after follow-up of patients for at least a median 6 months for the last patient included in intervention group which ranged from 13-36 months. The median DFS was 15 months (95% CI: 7.36 – 22.64) in the CRT group and 10 months (95% CI: 6.53 – 13.47) in the CTH group. The mean DFS was19.4 months (95% CI: 15.44 - 23.35) in the CRT group and 13.2 months (95% CI: 10.45-15.89) in the CTH group. CRT was associated with statistically significant longer DFS (p = 0.041) as shown in Figure 1. The estimated median OS was not reached in both treatment arms. The estimated mean OS was 27.9 months (95% CI: 24.75 -31.06) in the CRT group in comparison to 19.2 months (95% CI: 15.76 - 22.67) in the CTH group which was statistically significant (p = 0.023), represented in Figure 2.

Table 1: Patients' characteristics

Characteristic		CRT Group (N=41)	CTH Group (N=40)	p value
		No. (%)	No. (%)	
Sex				
	Male	27 (65.9%)	26 (65%)	0.9
	Female	14 (34.1%)	14 (35%)	
Age				
	≤60	29 (70.7%)	28(70%)	0.9
	>60	12 (29.2 %)	12 (30%)	
Grade				
	I	1(2.4%)	2(5%)	0.3
	II	40 (96.6%)	36(90)	
	III	0 (0)	2 (5%)	
Stage				
	2A	22 (53.7%)	18(45)	0.4
	2B	19 (46.3%)	22 (55%)	
Tumor size (T)				
	T2	10 (24.4%)	19 (47.5%)	0.03
	T3	31 (75.6%)	21 (52.5%)	
Lymph nodes (N)				
	N0	22 (53.7%)	18 (45%)	0.4
	N1	19 (46.3)	22 (55%)	
CA 19.9				
	≤37U/L	29 (70.7%)	25 (62.5 %)	0.8
	>37U/L	12 (29.3%)	12 (30%)	
	Unknown	0(0%)	3 (7.5%)	
Safety margin				
	Free (R0)	30 (73.2%)	29 (72.5%)	0.9
	Positive (R1)	11 (26.8%)	11 (27.5%)	

CRT: chemo-radiotherapy; **CTH**: chemotherapy; **CA19-9**: carbohydrate antigen 19-9; **R0**: free safety margin; **R1**: positive safety margin.

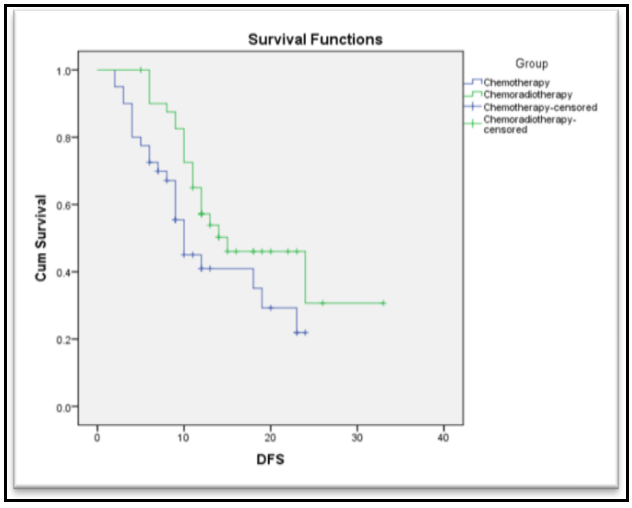

Figure 1: The Kaplan–Meier curve for disease-free survival (DFS)

According to the follow-up results, relapse developed in 12 (29.2%) patients in the CRT group *versus* 26 (65%) of the CTH group, which was highly significant (p = 0.001).

As regards the site of relapse, local recurrence developed in 1 (2.4%) patient in the CRT group with positive margin *versus* 6 (15%) patients in the CTH group. According to the systemic relapse, liver metastasis was the most common in both groups with 8 (19.5%) patients in the CRT group and 16 (40%) patients in the CTH group. The 2nd most common site of metastasis was the peritoneum which developed in 1 (2.4 %) case in the CRT group versus 3 (7.5 %) patients in the CTH group and the least site of metastasis was the bone which developed in only 2 (4.9%) patients in the CRT group *versus* 1 (2.5%) patient in CTH group.

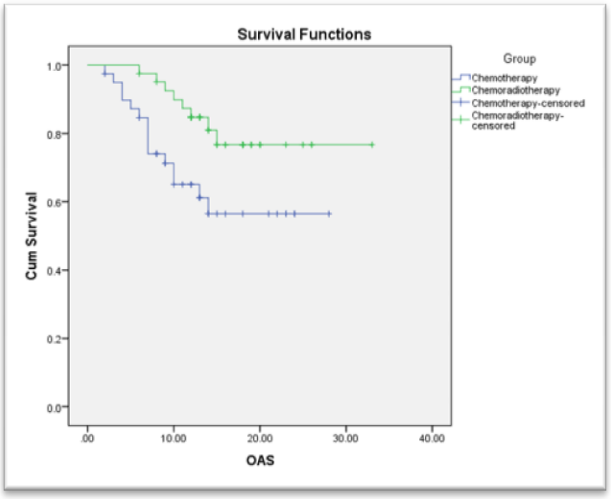

Figure 2: The Kaplan–Meier curve for overall survival (OS)

Among all predictors of patients and tumor characteristics, the only significant variables were age and stage. So these two variables entered the regression model which revealed that the stage is the only significant (p = 0.025) predictor of outcome (Table 2).

Table 2: Multivariate analysis for overall survival

Variable		HR	95% CI		P value
			Lower	Upper	
Stage					
	IIA	1			
	IIB	0.357	0.145	0.878	0.025
Age		1.049	0.99	1.1	0.07

CI: confidence interval; **HR**: hazards ratio.

The experimental treatment arm (CRT) was well tolerated and no deaths due to toxicity were reported. Main acute toxicities were hematological, anorexia, fatigue, nausea, vomiting, diarrhea, and abdominal pain and were slightly more frequent in the CRT arm and are summarized in Table 3. No grade 4 toxicities were developed. There was statistically significant difference between both groups as regards, anemia (p = 0.009), anorexia (p = 0.005), fatigue (p = 0.005), abdominal pain (p = 0.04) and hand and foot syndrome (p = 0.03).

Table 3: Acute treatment toxicities in the study groups

Toxicity	Grade	CRT group	CTH group	p value
		No (%)	No (%)	
Anemia	G1	9 (22)	7 (17.5)	0.009
	G2	10 (24.4)	1 (2.5)	
	G3	0	1 (2.5	
Leukopenia	G1	4 (9.8)	2 (5)	0.1
	G2	3 (7.3)	0	
Throbmocytopenia	G1	4 (9.8)	3 (7.5)	1
	G2	0	1 (2.5)	
Fatigue	G1	5 (12.2)	8 (20)	0.005
	G2	14 (34.1)	3 (7.5)	
	G3	2 (4.9)	0	
Anorexia	G1	5 (12.2)	8 (20)	0.005
	G2	14 (34.1)	3 (7.5)	
	G3	2 (4.9)	0	
Nausea	G1	10 (24.4)	12 (30)	0.3
	G2	3 (7.3)	0	
Vomiting	G1	5 (12.2)	6 (15)	0.48
	G2	6 (14.6)	0	
Abdominal pain	G1	4 (9.8)	2 (5)	0.04
	G2	11 (26.8)	3 (7.5)	
Weight loss	G1	3 (7.3)	1 (2.5)	0.7
	G2	1 (2.4)	2 (5)	
Diarrhea	G1	4 (9.8)	2 (5)	0.9
	G2	3 (7.3)	3 (7.5)	
Hepatic toxicity	G1	1 (2.4)	2 (5)	0.8
	G2	2 (5)	3 (7.5)	
	G3	1 (2.4)	1 (2.5)	
Hand & foot syndrome	G1	4 (9.8)	0	0.03
	G2	2 (4.9)	0	

CRT: chemo-radiotherapy; **CTH**: chemotherapy

DISCUSSION

There is no standard treatment for patients with pancreatic carcinoma in the adjuvant setting which included gemcitabine or fluoropyrimidine- based chemo-radiation with an addition of gemcitabine, continuous infusion fluorouracil, or fluorouracil+ leucovorin chemotherapy and chemotherapy alone with gemcitabine, fluorouracil+ leucovorin or capecitabine [10]. Both local and distant recurrences are common and the value of CRT in the adjuvant treatment of PC is still not confirmed [2].

In the current study, the estimated median OS was not reached in both treatment arms. However, the mean OS of the CRT group (27 months) which was significantly (p = 0.023) longer than that of the CTH group (19 months). These results are nearly similar to those of the GITSG trial for adjuvant fluorouracil-based CRT *versus* observation, where the median survival was 20 *versus* 11 months and 2-year survival rate was 42% *versus* 15%, respectively (P=0.03) [11]. On the contrary, the EORTC randomly assigned cases to adjuvant CRT *versus* observation but without significant difference in survival between both groups, with median survivals of 17 and 13 months in the treatment and observation groups, respectively, and with 5-year survival estimates of 23 % and 10%, respectively. This may be attributed to lack of quality control of radiotherapy, low total dose and suboptimal schedules of fluorouracil-based CRT [12]. Our results were similar to that of RTOG 97-04 trial, which compared between gemcitabine *versus* fluorouracil pre and post fluorouracil-based radiotherapy. The median survival times were 20.5 months *versus* 17.1 months, respectively (p= 0.12) [13]. Our trial revealed more survival due to a high dose of radiotherapy according to safety margin with 3DCRT.

Patients' treatment with the gemcitabine/capecitabine drug combination is supported by the most recent phase III (ESPAC-4) trial which compared this combination to gemcitabine. It resulted in a statistically significant 2.5 months improvement in survival in the combination regimen. Median survival for patients treated with gemcitabine/capecitabine was 28 months and 25.5 months for those treated with

gemcitabine alone with a hazard ratio of 0.82 (p = 0.032) [17], which is consistent with our findings.

Van Laethem *et al.* conducted phase II trial comparing CRT *versus* CTH and found that the median OS was 24.4 months in the control arm and 24.3 months in the experimental arm, which was not significant [14]. However, our trial revealed a significant difference which may be due to extended duration of treatment up to 6 months. The Median DFS of this phase II trial was 10.9 months in the control arm and 11.8 months in the experimental arm. Our results revealed a mean DFS of 19 ms for the CRT group and 13 months in the CTH group with a statistically significant p-value of 0.041 because of 5% of our cases had grade III in both arms and most of cases were grade II

As regards our trial, the median DFS was 15 months in the CRT group and 10 months in the CTH group (p=0.041). In the CONKO-001 trial, the median DFS was 13.4 months in the gemcitabine group compared to 6.9 months in the observation group (P=0.001). But the OS in our CTH group was19 months which is less than that in CONKO-001 trial, 22.1 and 20.2 months in the gemcitabine group and the observation group, respectively. This was statistically non-significant that may be because 55% of cases were in stage IIB and 27.5% with positive safety margin [15]. The ESPAC-3 trial resulted in median OS of 23 months in cases treated with fluorouracil/folinic acid, while those treated with gemcitabine had a median OS of 23.6 months [16]. The aforementioned, both were less than OS obtained in our CTH group attributed to advanced stage of disease as 55% of cases with stage IIB, 27.5% with positive margin and 30% with elevated CA19-9.

In our trial, the CRT treatment protocol was tolerated and the acute toxicity was acceptable but slightly more frequent than in the CTH control group. Regarding the hematological toxicity, it was similar to the toxicity of CONKO-001 trial [15].

In all CRT trials, the toxicities were tolerated with different grade but in the RTOG 97-04 trial, grade 4 hematological toxicity developed with statistically significant difference between both arms, despite complete treatment [13]. Noteworthy, a Japanese phase III trial developed grade 3 and 4 leucopenia and also resolved with supportive treatment [18].

In the current study, non-hematological toxicities developed with different grades from 1 to 3 which were more in CRT group but well tolerated. This may be attributed to the good performance status, relatively younger median age and the strict follow up with weekly assessment and supportive treatment. In RTOG 97-04 trial, non-hematological toxicity was common in the fluorouracil group with a statistically significant value; however, all cases completed treatment. In 2010 Van Laethem *et al.,* compared CRT versus CTH and found that toxicity was common in CRT group with a significant difference in abdominal pain, anorexia and gastritis [14]

The effect of CRT on local control was detected in our trial as the local recurrence developed in only 1case (2.4%) in the CRT group versus 6 cases (15%) in the CTH group. This was attributed to the effect of radiotherapy with high quality and high dose according to safety margin. Alike, the randomized phase II trial by Van Laethem *et al.* revealed that the rate of local recurrence alone was lower in the CRT arm than CTH (11% versus 24%) [14]. Although, they included only R0 cases and we included R0 and R1 cases. Also in RTOG 97-04, the local recurrence rate was only 26%; however, the percentage of cases with T3/T4 disease was 75%, positive LN was 66% and positive margins was 34% [13]. Our results differed from that of the EORTC and ESPAC-1 trials due to suboptimal CRT techniques and omission of RT in some ESPAC-1 cases, resulting in higher rate of local recurrence (36- 62%) in spite of the fact that most cases had T1/T2 disease (EORTC) and negative margins (EORTC and ESPAC-1). Our CTH group revealed higher rates of local recurrence as in the CONKO-001 (34-41%) and ESPAC-3 (63%) trials [19].

In the phase II trial of adjuvant gemcitabine alone *versus* gemcitabine-based CRT that was conducted by Regine *et al*., the rate of distant metastases was similar in both arms (40% in the CTH arm and 42% in the CRT arm) [13]. On the contrary, in our trial, the systemic relapse developed in 26.8% of CRT group versus 50% in the CTH group. This may be due to the duration of the protocol of treatment, which was 6 months in our trial *versus* 4 months only in the comparative trial. In the RTOG 97-04 trial, distant relapse was more than 70% in both groups, which was more than that obtained in our research [13].

In this study, the only significant variables were age and stage. Subsequently, these two variables entered the regression model whereas the stage revealed as the only significant predictor of the outcome with P= 0.025. On the other hand, in RTOG 97-04 trial, nodal status was strongly correlated with survival (p= 0.003), tumor diameter, and safety margin status didn't affect survival as (p= 0.08). However, tumor stage was imbalanced between the arms, and was not a significant factor in multivariate analysis [13].

Conclusion

Adjuvant CRT, using capecitabine and 3D conformal radiotherapy with initial and subsequent systemic gemcitabine, is tolerable, effective, and offers better local control than chemotherapy (gemcitabine) only. The CRT protocol showed a significantly better DFS, OS and acceptable toxicity compared to CTH alone. However, further studies with larger number of cases are needed.

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