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Impact of Chemoradiotherapy versus Chemotherapy on Operability and Survival in Patients with Locally Advanced Surgically Inoperable Pancreatic Cancer: A Randomized Trial

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Authors' contributions

This work was carried out in collaboration among all authors. Author FI designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors ME, DA and AA managed the analyses of the study. Author STE managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: To determine the tolerability and efficacy (as regards response, toxicity, resectability, progression free survival, and overall survival) of chemotherapy alone versus induction chemotherapy then concurrent 3D conformal radiotherapy.
Study Design: This was a prospective double arm study.
Place and Duration of Study: Department of Clinical Oncology and Nuclear Medicine, Mansoura University Hospital, Mansoura and Meet Ghmmr oncology centre, Egypt, between May 2017 and June 2019.
Methodology: Between May 2017 and June 2019, 58 patients with biopsy-proven localized unresectable pancreatic cancer were treated either with chemotherapy alone (n=27) or chemotherapy followed by chemoradiotherapy (n=31). Radiation therapy was delivered with a dose

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of 50.4 Gy in a single fraction of 1.8 Gy using 3D conformal radiotherapy and concurrent CT was typically given with capecitabine at a dose of 825 mg/m2 twice daily orally from Saturday to Wednesday throughout the whole course of radiotherapy. They received induction chemotherapy gemcitabine-cisplatin in arm I (6 cycles) and arm II (4 cycles), {gemcitabine dose of 1000 mg/m^2, cisplatin dose of 50 mg/m^2D1+D15 every 4 weeks}. Surgery was done for responders.

Results: Overall response rate was 66.7% & 96.8% in chemotherapy and chemoradiotherapy groups respectively with statistically significant difference; no complete was achieved (P=0.004). Four patients (14.8 %) in group1and ten patients (31.25%) in group 2 became resectable with no statistical significant difference between both groups (P=0.121). No statistically significant difference in the occurrence of toxicities between the two groups except for diarrhea and stomatitis that were significantly higher in chemoradiotherapy group. There were no reported grade 4 toxicities. The median follow-up time was 18 months. Median progression free survival was statistically significant and higher in chemoradiotherapy group than in chemotherapy group (12 & 9 months respectively); P = 0.024. Median overall survival was higher but not statistically significant in chemoradiotherapy (22 months) versus 14 months in chemotherapy group; P = 0.054.

Conclusion: concurrent chemoradiotherapy using capecitabine and 3D conformal radiotherapy with initial systemic gemcitabine plus cisplatin is tolerable, effective and offers good local control for patients with locally advanced pancreatic cancer. This protocol showed a significantly better overall response and progression free survival but no overall survival benefit.

Keywords: Pancreatic cancer; concurrent chemo-radiotherapy; 3D conformal radiotherapy; toxicity; efficacy.

1. INTRODUCTION

The role of neoadjuvant treatment (NAT) in pancreatic adenocarcinoma (PDAC) is still under debate because of shortage of data in comparison with other gastrointestinal cancers, in which the role of NAT is more well-defined [1]. Pancreatic cancer is a treatment challenge with a bad prognosis. In 2018, there were about 55,000 new cases in the United States and almost 500,000 worldwide. The annual number of deaths from pancreatic carcinoma nearly equals the annual incidence. The integration of surgery, chemotherapy, and radiotherapy has resulted in more advances in understanding of the disease and has improved the outcomes for those patients [2].

Surgery for locally advanced pancreatic cancer following neoadjuvant treatment is still debated. 154 resected borderline (BR)/locally advanced patients after NAT and suggested that every patient who receives NAT for BR/LA PDAC without signs of disease progression should be explored for possible resection, as it is difficult radiologically to define regression criteria. Moreover, they showed that surgical resection had a positive impact on survival for all values of CA 19-9 despite the fact that higher levels of CA 19-9 have been associated with worse prognosis [3].

Most cases with locally advanced; unresectable or radiographic findings for extra pancreatic disease, so an initial period of chemotherapy rather than immediate radiation therapy (RT) or chemoradiotherapy (CRT) is suggested. This recommendation is consistent with consensus-based guidelines from the ASCO [4] and the NCCN [5].

2. PATIENTS AND METHODS

A phase II prospective study included patients with localized unresectable pancreatic cancer who are treated in the Department of Clinical Oncology & Nuclear Medicine at Mansoura University Main Hospitals and Meet Ghmmr Oncology Centre in the period between May 2017 and June 2019.

2.1 Selection of Patients

Pathological evidence of carcinoma of the pancreas, radiological evidence of locally advanced pancreatic cancer (T3 or T4) with or without radiologically evident positive lymph nodes, Eastern Collaborative Oncology Group (ECOG) performance status ≤ 2, age > 18 years, adequate bone marrow (hemoglobin ≥ 10 gm/dl, platelet ≥ 100,000/mcl, WBCs ≥ 3000/mcl provided that absolute neutrophilic count (ANC) ≥ 1500/mcl), and adequate renal and hepatic function (creatinine clearance > 50 ml/min and bilirubin ≤ 1.5 mg/ml). Patient exclusion criteria: patients with active concurrent or previous malignancies, local recurrence, metastatic

disease, and or severe active comorbidity will be excluded from the study.

2.2 Patients Assessment

Pretreatment evaluation included a complete history and physical examination, complete blood count, liver and renal function tests, carbohydrate antigen 19-9 (CA19-9), biopsy with or without endoscopic ultrasound (EUS), Base line CT or MRI abdomen and pelvis, Chest X- ray or CT chest if there is suspicious lesion and bone scan (if there is bony symptoms).PET/CT was considered in high risk patients to detect distant metastases. Performance status was assessed according to ECOG performance status scale [6].

2.3 Treatment Details

Fifty eight patients were fulfilled the inclusion criteria; Patients were randomly assigned to receive one of the two treatment arms: Arm I (n=27): patients were subjected to chemotherapy alone (Gemcitabine plus Cisplatin) for 6 cycles. Arm II (n=31): patients were subjected to induction chemotherapy (Gemcitabine plus Cisplatin) for 4 cycles followed by 3D conformal radiotherapy concurrent with Capecitabine for 5-6 weeks (The overall treatment period was 6 months). Gemcitabine at a dose of 1,000 mg/m² over 30 minutes days 1 and 15 plus Cisplatin 50 mg/m² over 1 hour given on days 1 and 15 of a 4-week cycle. Capecitabine was given at a dose of 825 mg/m² twice daily orally from Saturday to Wednesday throughout the whole course of radiotherapy. Conformal three dimensional (3D) planned radiotherapy was delivered at a dose of 50.4 Gy over 28 fractions over 5.5 weeks. The response was assessed by CT chest, abdomen, and pelvis, the interval between the end of CCRT and surgery ranged from 6 to 10 weeks. The non-metastatic surgically fit patients (14 patients; Arm I (n=4); Arm II (n=10)) had radical surgery according to the surgeon's decision.

2.4 Toxicity Measurement

Patients were evaluated each cycle during chemotherapy treatment, and five times during chemo-radiation to assess acute toxicity. Toxicities were assessed and recorded according to the Common Terminology Criteria for Adverse Event (CTCAE) v4.0.

2.5 Follow Up

Clinical examination was performed at each follow-up visit, CT chest, abdomen, and pelvis was done after completing neoadjuvant treatment, post-surgical intervention, and then every 3 months or when clinically indicated. Patients who developed a progressive or metastatic disease were shifted to second-line chemotherapy and were followed for at least 6 months or till death.

2.6 Study End Points

The primary endpoints were to evaluate response rate(RR), potentiality for resectability and toxicity. The secondary endpoints included evaluation of progression-free survival (PFS) which defined as the time from diagnosis until first evidence of tumor progression and overall survival (OS) which is defined as the time from diagnosis to death from any cause or last follow-up.

2.7 Statistical Analysis and Data Interpretation

Data were analyzed using IBM SPSS software package version 25.0. Qualitative data were tabulated using number and percent. After testing normality using the Kolmogrov-Smirnov test, quantitative data were described using median (minimum and maximum) for non-parametric data and mean, the standard deviation for parametric data. Significance was judged at the (0.05) level. Cox regression (or proportional hazards regression) is used for investigating the effect of several variables upon the time a specified event takes to happen. Cumulative hazard at a time t is the risk of dying between time 0 and time t, and the survivor function at time t is the probability of surviving to time t. The coefficients in a Cox regression relate to hazard; a positive coefficient indicates a worse prognosis and a negative coefficient indicates a protective effect of the variable. Kaplan-Meier used to calculate overall survival and progression free survival times. Univariate analysis was done using log-rank test to calculate the effect of pathologic types and treatment response on median survival times.

3. RESULTS

3.1 Patients and Tumor Characteristics

The baseline characteristics of the 58 patients and their tumors are summarized in (Tables 1 and 2). This study involved 58 patients after exclusion of 10 patients who did not match

eligibility criteria. They were 40 male and 18 female patients with mean age (years) ± SD OF 55.1 ± 10 years. They were divided into two treatment groups: Group 1 (Chemotherapy alone): n=27& Group 2 (Chemotherapy followed by chemoradiotherapy): n=31. The two groups were comparable regarding patient characteristics. The most common site for tumor in both groups was head of pancreas. Regional lymph nodes were involved in 16 patients (59.3%) in the 1st group, while 18 patients (58.1%) in the 2nd group.

3.2 Tumor Response

Regarding response rate for patients in 1st group, 13 patients (48.1%) achieved partial response (PR), while complete response (CR) was not detected. Five patients (18.5%) had stable disease (SD) ,18 patients (66.7%) had disease control (DC). Disease progression (PD) was documented in 9 patients (33.3%). In the 2nd group, no CR was detected but PR was achieved in 18 patients (58.1%). Twelve patients (38.7%) had SD, 30 patients (96.8%) had disease control (DC), and disease progression (PD) was documented in 1 patient (3.2%). We noticed a statistically significantly higher proportion of overall response in Group 2 vs Group 1 (p value = 0.006) (Table 3). As regard resectability after neoadjuvant treatment, four patients (14.8 %) in CHT group and ten patients (31.25%) in CRT group became resectable with no statistical significant difference between both groups (P=0.121).

3.3 Survival Results

Median PFS was 9 months in the 1st group (95% Confidence Interval, 7.7-5.10.3 months) and 12 months for the 2nd group (95% Confidence Interval, 11.4-12.6 months). PFS was statistically significant and higher in CRT group (P value = 0.024) (Fig. 1). The median OS was 14 months for the 1st group (95% Confidence Interval, 10.96-17.04 months) in comparison to 22 months in the 2nd group (95% Confidence Interval, 15.96 - 28.04 months). However, this higher median OS in group 2 vs group 1 didn't achieve statistical significance (P value = 0.054) (Fig. 2).

Table 1. Baseline patients characteristics

Characteristic	Group 1 (n=27)	Group 2 (n=31)	P-value
Age (years):			
Mean ± SD	54.6 ± 10.3	55.6 ± 9.9	0.722
Age Category:			
< 60 years	20 (74.1%)	20 (64.5%)	0.433*
≥ 60 years	7 (25.9%)	11 (35.5%)	
Sex:			0.829*
Male	19 (70.4%)	21 (67.7%)	
Female	8 (29.6%)	10 (32.3%)	
ECOG:			0.568**
0	16 (59.3%)	16 (51.6%)	
1	7 (25.9%)	12 (38.7%)	
2	4 (14.8%)	3 (9.7%)	
Positive -HCV	9 (33.3%)	7 (22.6%)	0.361
Comorbidity:			
Presence of any comorbidity	10 (37%)	12 (38.7%)	0.896 *
DM	9 (33.3%)	7 (22.6%)	0.361*
Hypertension	3 (11.1%)	7 (22.6%)	0.311**
IHD	2 (7.4%)	1 (3.2%)	0.593**
Symptom:			
Pain	16 (59.3%)	26 (83.9%)	0.036*
Jaundice	22 (81.5%)	18 (58.1%)	0.055*
Weight loss	3 (11.1%)	8 (25.8%)	0.154*
Vomiting	3 (11.1%)	3 (9.7%)	1.000**
Anorexia	0 (0%)	5 (16.1%)	0.055**

ECOG: Eastern Collaborative Oncology Group; DM: Diabetes melli

Table 2. Tumour characteristics

Characteristic	Group 1 (n=27)	Group 2 (n=31)	P-value
Tumor site:			0.769**
Head	16 (59.3%)	17 (54.8%)	
Body	4 (14.8%)	8 (25.8%)	
Tail	2 (7.4%)	2 (6.5%)	
Neck	5 (18.5%)	4 (12.9%)	
CA 19-9:			
Median (IQR)	450 (60-1000)	131 (12-600)	0.088***
Range	2-5000	1-2900	
CA 19-9 Category:			
< 169	12 (44.4%)	17 (54.8%)	0.430*
≥ 169	15 (55.6%)	14 (45.2%)	
Pathology			0.453**
Adenocarcinoma	22 (81.5%)	28 (90.3%)	
Others	5 (18.5%)	3 (9.7%)	
Grade			0.933**
Well-differentiated	3 (11.1%)	4 (12.9%)	
Moderately differentiated	10 (37%)	13 (41.9%)	
Poorly differentiated	14 (51.9%)	14 (45.2%)	
N stage			0.927*
N0	11 (40.7%)	13 (41.9%)	
N1	16 (59.3%)	18 (58.1%)	

*P-value: *Chi-square test; ** Exact test; ***Mann-Whitney test*

Table 3. Response rate

Response	Group 1 (n=27)	Group 2 (n=31)	P-value
CR	0 (0%) a	0 (0%) a	0.006
PR	13 (48.1%) a	18 (58.1%) a	
SD	5 (18.5%) a	12 (38.7%) a	
PD	9 (33.3%) a	1 (3.2%) b	
Overall response	18 (66.7%)	30 (96.8%)	0.004

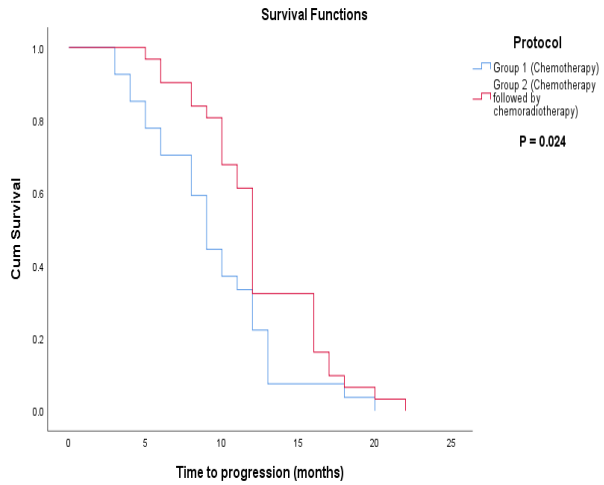

Fig. 1. Kaplan Meier curve showing PFS in both groups

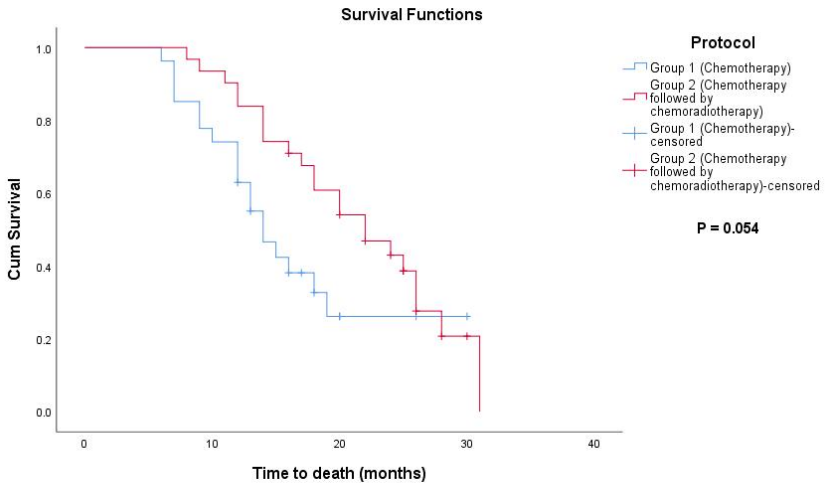

Fig. 2. Kaplan Meier curve showing OS in both groups

Table 4. Prognostic factors of overall survival on univariate and multivariate analysis:

Predictor	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age				
<60	1.21 (0.625-2.34)	0.675	1.20 (0.56-2.59)	0.636
≥60				
Sex				
Male	1.37 (0.71-2.65)	0.343	1.81 (0.835-3.91)	0.133
Female				
CA 19-9				
> 169	1.09 (0.58-2.05)	0.781	1.66 (0.825-3.35)	0.155
<169				
Treatment modality				
Group 2 (CRT)	1.85 (0.964-3.54)	0.064	1.13 (0.505-2.52)	0.769
Group 1 (CHT)				
Response				
non- PD	9.15 (3.91-21.39)	<0.001	13.88 (4.71-40.88)	<0.001
PD				

Univariate analysis of overall survival; age, CA 19-9 < 169, responders and receipt of CRT were prognostic factors for better survival. Multivariate analysis revealed that the pattern of treatment modality was a predictor for better survival. Our results showed that patients who received chemotherapy only had shorter OS than those who received CRT. This difference was not statistically significant (P value = 0.769). Multivariate analysis also revealed that tumor response is a predictor for better survival. Our results showed that patients with disease progression had shorter OS than those with stable disease or tumors responding to treatment. This difference was statistically significant (P value < 0.001) Table 4.

3.4 Toxicities of Chemotherapy and CCRT

Details of acute induction chemotherapy and CCRT-induced toxicities are listed in (Tables 5 and 6). No statistically significant difference in the occurrence of hematological side effects between the two groups. As regard non hematological toxicities, no statistically significant difference in the occurrence of gastrointestinal side effects (vomiting, abdominal pain, ascites and Increased bilirubin) between the two groups but a statistically significant difference in the occurrence of diarrhea and stomatitis was observed.

Table 5. Hematological toxicities

Hematological side effect	Group 1 (n=27)	Group 2 (n=31)	P-value
Anemia			0.210
G1	12 (44.4%)	18 (58.1%)	
G2	11 (40.7%)	10 (32.3%)	
G3	3 (11.1%)	0 (0%)	
Leucopenia			0.434
G1	2 (7.4%)	6 (19.4%)	
G2	8 (29.6)	7 (22.6%)	
G3	1 (3.7%)	0 (0%)	
Thrombocytopenia			0.971
G1	9 (33.3%)	11 (35.5%)	
G2	7 (25.9%)	8 (25.8%)	
G3	0 (0%)	1 (3.2%)	

Table 6. Non-hematological toxicities

Non-hematological side effect	Group 1 (n=27)	Group 2 (n=31)	P-value
Vomiting			0.871
G1	5 (18.5%)	5 (16.1%)	
G2	3 (11.1%)	3 (9.7%)	
G3	1 (3.7%)	0 (0%)	
Diarrhea			0.018
G1	2 (7.4%)	8 (25.8%)	
G2	1 (3.7%)	6 (19.4%)	
Stomatitis			0.039
G1	0 (0%)	4 (12.9%)	
G2	5 (18.5%)	1 (3.2%)	
Abdominal pain			0.343
G1	1 (3.7%)	5 (16.1%)	
G2	4 (14.8%)	5 (16.1%)	
Ascites			1.000
G1	0 (0%)	1 (3.2%)	
G2	0 (0%)	1 (3.2%)	
Increased bilirubin level			0.502
G1	3 (11.1%)	5 (16.1%)	
G2	3 (11.1%)	1 (3.2%)	
Fatigue			0.923
G1	4 (14.8%)	6 (19.4%)	
G2	6 (22.2%)	8 (25.8%)	
G3	4 (14.8%)	3 (9.7%)	
Nephropathy			0.851
G1	4 (14.8%)	5 (16.1%)	
G2	1 (3.7%)	0 (0%)	
Neuropathy			0.028
G1	5 (18.5%)	12 (38.7%)	
G2	2 (7.4%)	7 (22.6%)	

3.5 Surgery

For those patients who converted to be resectable after full course of CTH or CRT are subjected to either: The classic Whipple procedure involves removal of the head and uncinate process of the pancreas, duodenum, proximal (15 cm) of jejunum, gallbladder, common bile duct, and distal stomach, with anastomosis of the common hepatic duct and the

remaining pancreas and stomach to the jejunum. Distal pancreatectomy was performed in patients with resectable cancer in the distal body or tail of the pancreas. The spleen usually is removed as well. Criteria of resectability include Patent SMV and portal vein, clear fat planes around celiac artery and SMA, less than 180 degree abutment of SMA and no distant metastases.

4. DISCUSSION

Pancreatic cancer is the 7th leading cause of cancer mortality in the world (about 432,000 deaths/year) and its incidence is increasing worldwide, which may reflect rapid population growth and aging. Pancreatic cancer is one of the most lethal malignancies, however there is a gradual improvement in survival in the last 2 decades and increasing the 5-year survival rate from 4% to 9%. Advances in chemotherapy has a great impact on survival at any stage of disease. In terms of resectable pancreatic cancer, the role of adjuvant therapy has been established and a treatment strategy of neoadjuvant therapy is emerging [7]. This poor prognosis is mainly due to late diagnosis, with only 20% of patients with PDAC eligible for surgery. Complete surgical resection of localized PDAC followed by 6 months of adjuvant chemotherapy is the only recognized standard of care that has been shown to improve patient survival [8].

The current study was conducted to evaluate whether a good quality of combined-modality therapy can be achieved safely in locally advanced pancreatic cancer. The primary end points were to evaluate response rate (RR), potentiality for resectability and toxicity. while The Secondary end points included evaluation of progression free survival (PFS) and overall survival (OS). In this study, patients who received chemotherapy alone, ORR was achieved in 66.7% of patients. Partial response rate was attained in 48.1% of patients (13 patient), while SD was achieved in 18.5% of patients (5 patients). Progression occurred in 9 patients (33.3%). On the other hand; group 2 showed ORR 96.3% (30 patients), partial response achieved in 58.1% of patients (18 patient), while SD was achieved in 3.2% of patients (1 patient). A significantly higher proportion of overall response in Group 2 vs Group 1 (p value = 0.006).

These results were better than the results of a retrospective study done by Girard et al; 2009 on 18 patient with locally advanced pancreatic cancer utilizing gemcitabine administered twice weekly at a dose of 40 mg/m² concurrent with total dose of 40-50.4 Gy delivered using 1.8-2.0 Gy daily fractions, followed by maintenance systemic chemotherapy with gemcitabine, at a dose of 1000 mg/m² administered weekly for 3 weeks with 1-week rest until disease progression or unacceptable toxicity developed. The response rate was 5% complete response, 22% partial responses, 50% stable diseases and 23% progressive disease [9]. The higher dose of gemcitabine plus cisplatin and capecitabine given with radiation may explain the better results of our study. In LAP07, an international, open-label, phase 3 randomized trial, 449 patients were enrolled between 2008 and 2011. Eighteen patients (4%) underwent a curative-intent resection, 6 before the second randomization (these were excluded from the study) and 12 after the completion of protocol; 8 [6%] after chemotherapy and 4 [3%] after chemoradiotherapy (P = 0.25). Eleven patients (2.5%) had an R0 resection, 2 (0.5%) had an R1 resection, and 5 (1.1%) had unknown margins status [10]. In comparison with our study, resectability rate was higher and this could be attributed to small sample size. MD Anderson Cancer Center published their neoadjuvant treatment results using two different treatment strategies. In their first trial, patients received neoadjuvant radiotherapy concurrent with gemicitabine weekly followed by surgery. Eighty six patients treated in the period between 2004 and 2006; 64 (73%) underwent resection with R0 resection rate of 89% and complications were 9% [11]. In the 2nd trial; induction chemotherapy then CRT was used to decrease distant metastases and increase OS. Ninety patients were studied in this trial. Cisplatin plus gemcitabine were given for 2 cycles before concurrent CRT. Gemcitabine was used as sensitizer with radiotherapy. 62 patients were resectable (radiologically) and were explored surgically with resection rate of 66%. Positive margins were detected in 1 patient (R1 resection rate of 4%) and nodal involvement rate was 58% in successfully resected patients [12]. Our study showed higher median OS in group 2 but did not achieve statistically significant difference. While PFS was statistically significant and higher in group 2 patients treated with chemotherapy followed by CRT compared to patients treated with chemotherapy alone (OS: 14 versus 22 months, p = 0.054), (PFS: 9 versus 12 months, p = 0.024). GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) Phase II and III

studies compared chemoradiation versus continuous chemotherapy after a at least 12 weeks of 5-FU or gemcitabine-based chemotherapy. About 30% of patients became metastatic after initial chemotherapy. For patients who responded; radiation to 5500 cGy with concurrent continuous infusion 5-FU improved survival compared to continued chemotherapy with median survival of 15.0 versus 11.7 months, P=0.0009 [13]. These results were comparable to the study conducted at MD Anderson Cancer Center (MDACC); 300 patients received upfront chemoradiation (30 Gy concomitant with 5-FU, capecitabine, or gemcitabine) or a median of about 2.5 months of induction chemotherapy followed by CRT. Selected use of chemoradiation after initial chemotherapy was associated with improved survival; median of 11.9 months compared to upfront chemoradiation; median survival 8.5 months (P<0.001) [14]. This concept of the importance of the induction phase is confirmed also by Gillmore et al; 2010 who compared induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy from the start. A multi-Centre retrospective analysis of 48 patients with biopsy proven locally advanced pancreatic cancer treated with CRT from the start (n=24) or starting with induction chemotherapy (n=24) in four regional oncology centers in the UK between March 2000 and October 2007. The prescribed radiotherapy dose was 4500-5040 cGy in 25-28 fractions. The disease control rate was 73.4% vs. 81.3%. The median overall survival was 13 versus. 17 months [15].

Finally, this study has several limitations, being single-center design, with a small number of patients, with limited follow-up time. Further larger phase III comparative trial is needed for confirmation of the efficacy and standardization for the treatment protocol.

5. CONCLUSION

The preliminary data suggested a good efficacy of the treatment design with acceptable adverse-event rates which may encourage for larger multicentric phase 3 trial with long follow up period to investigate the same regimen before standardizing it.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Informed consent has been written before patients' enrolment in the trial.

ETHICAL APPROVAL

The study was approved by IRB unit at the faculty of medicine, Mansoura University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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