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Modified-FOLFIRINOX-Losartan Followed by Chemoradiotherapy for Locally Advanced Pancreatic Cancer: A Phase II Study

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ABSTRACT

Background: At presentation only 20% of pancreatic cancer patients are defined resectable due to advanced initial disease stage.

Objective: To study the clinical outcome of patients with unresectable locally advanced pancreatic cancer (LAPC) after neoadjuvant modified FOLFIRINOX-losartan followed by chemoradiotherapy.

Methods: This phase II clinical trial was carried out on 50 patients with newly diagnosed surgically unresectable LAPC. Patients had Performance status (PS) ≤ 1 and normal organ functions. They arranged to receive 3 cycles of modified FOLFIRINOX with losartan taken orally every day followed by chemoradiotherapy (CCRT).

Results: Out of the 50 patients, thirteen (26%) patients had surgery; R0 resection achieved in 6 of 13 patients. After median follow-up duration of 20.25 months (6.0-34.5 months), the median overall survival (OS) was 21 months (95% CI,)10.200–31.800). Patients who had surgical resection had longer OS of 24 months (95% CI, (16.363 – 27.637) compared to those who didn't have resection the mean OS was 14 months (95% CI, (9.205 – 18.795) (P=0.271). The patients who achieved CR after modified FOLFIRINOX had longer survival of 33 months (95% CI, 19.918 – 46.082) compared to those who had PR and SD. Each has median OS of 13 months (95% CI, 6.768 – 19.232), (11.718 – 14.282) respectively (P=0.040*). The patients who achieved CR after CCRT had longer OS (median not reached) compared to those who had PR, SD and PD; median OS was 24, 14 and 8 months respectively and 95% CI was (6.761 – 41.239), (11.022 – 16.978), and (4.080 – 11.920) respectively (P=0.001*).

Conclusion: Modified-FOLFIRINOX/losartan protocol followed by CCRT had high response, feasible and could improve patients' outcomes in LAPC.

Keywords: LAPC, Modified-FOLFIRINOX-Losartan, Chemoradiotherapy.

INTRODUCTION

PDAC or pancreatic ductal adenocarcinoma is a dismal prognosis malignant neoplasm [1]. Its management continues to be challenging. Surgery is the only curative treatment modality but with 5 years OS rate of only 10–20% [2]. So, participation in clinical trials is preferred. Preoperative chemotherapy followed by chemoradiation and then surgery appears to be optimal option [3]. Also, combination of intensive chemotherapy and radiation with other pharmacological drugs like the blood-pressure modulating drug losartan may produce remarkable results [2].

Preclinical studies suggested that manipulating renin angiotensin system (RAS) could have anticancer effect in patients with PDAC, as it is possibly mediating cell growth and metabolism. Inhibition of RAS activity achieved by losartan, could decrease the oncogenic potential of malignant cells and change the tumor internal microenvironment and enhance the delivery of cytotoxic systemic therapy [4].

We aimed to study the surgical resectability, response and survival of patients with LAPC after neoadjuvant modified FOLFIRINOX-losartan followed by chemoradiotherapy.

PATIENTS AND METHODS

This phase II prospective clinical study was carried out on 50 patients with newly diagnosed surgically unresectable LAPC during the period from April 2020 to April 2023.

Inclusion criteria: histopathological diagnosis of PDAC, patients age 18-70 years old of both sexes, PS ≤ 1 [5], with average renal, liver and bone marrow functions.

Exclusion criteria: Stage IV disease [6], previous irradiation to upper abdominal region, and patients have baseline hypotension, defined as systolic blood pressure lower than 100 mm Hg.

Methods: Included patients underwent baseline evaluation; physical examination, and staging imaging; CT or MRI pancreatic protocol, CT chest and pelvis with contrast ± PET/CT. LAPC patients with unresectable disease by NCCN definition [7].

Baseline Lab evaluation: CEA, CA19-9, CBC, renal and liver functions. Patients were arranged to receive 3 months of modified FOLFIRINOX prior to CCRT, with losartan taken orally every day 25 mg/ day as a starting dose, if it was tolerable during the first week. It would be increased to 50 mg/day and continued until the completion of the last cycle. Assessment of blood pressure, K, and Na level were done every cycle. Restaging with CTs with contrast, CEA and CA 19.9 were requested after 3 cycles of modified FOLFIRINOX-losartan. Toxicity of treatment protocol were assessed by CTCAE, Version 5.0 [8].

Radiological responses to chemotherapy were evaluated by RECIST criteria version 1.1 [9]. Long-

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course conventionally fractionated 3DCRT was delivered at a dose of 50.4 Gy/28 fractions, concurrent with capecitabine (dose: 825 mg/m^2 orally daily divided in two doses approximately 12 hours apart given Sunday through Thursday). After completion of CCRT, restaging with CT scans was evaluated. If the tumor became resectable, surgery was performed.

Ethical approval:

An ethical approval from Faculty of Medicine Committee, Menoufia University (IRB 5/2020ONCO23) was obtained, and all participants provided a written informed consent. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. The Kolmogorov–Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). Statistical significance was set at the 5% level. The Fisher's exact test, Monte Carlo correction, and Student's t test were used for data analysis. P value < 0.05 was considered significant.

RESULTS

The mean (± SD) age of the studied cases was 52.06 ± 6.80 years. Thirty-three cases (66%) were males. Most of the studied patients had grade II tumors (78%).Thirty-eight cases (76%) had tumor location at head. The mean (± SD) tumor size was 44.34 ± 7.41 mm (Table1), CA 19.9 ranged between (23.0 and 10000) with a mean (± SD) of 642.0 ± 1653.0 and the median (IQR) was 87.0 (43.0 – 654.0).

Table (1): Baseline data of the studied patients:

Data		No.	%
Age	<53years	23	46.0
	≥53years	27	54.0
	Median (IQR)	**53.0** (49.0 – 58.0)	
Sex	Female	17	34.0
	Male	33	66.0
ECOG PS	0	15	30.0
	1	35	70.0
Smoking	Non-smoker	33	66.0
	Smoker	17	34.0
Pathological grade	Grade II	39	78.0
	Grade III	11	22.0
Tumor site	Head	38	76.0
	Tail and body	12	24.0
Tumor size (mm)	Min. – Max.	29.0 – 59.0	
	Mean ± SD.	44.34 ± 7.41	
Vascular involvement	Arterial	20	40.0
	Venous	13	26.0
	Both	17	34.0

IQR: Interquartile Range SD: Standard deviation

All patients received 3 full cycles (3 months) of induction chemotherapy (Modified FOLFIRINOX and losartan) with completion rate 96%. Dose reduction of modified FOLFIRINOX was done in 4% of all patients. All continued on the study. No patients had progression during chemotherapy. All patients proceeded to CCRT, and all received long-course CCRT.

The most common side effects during modified FOLFIRINOX-losartan induction were diarrhea (12%), febrile neutropenia (10%), and peripheral neuropathy (10%) (Figure 1). GIII toxicity of modified FOLFIRINOX in the form of fever neutropenia and diarrhea were documented in 3 patients. There was no reported grade IV toxicity during treatment (Table 2).

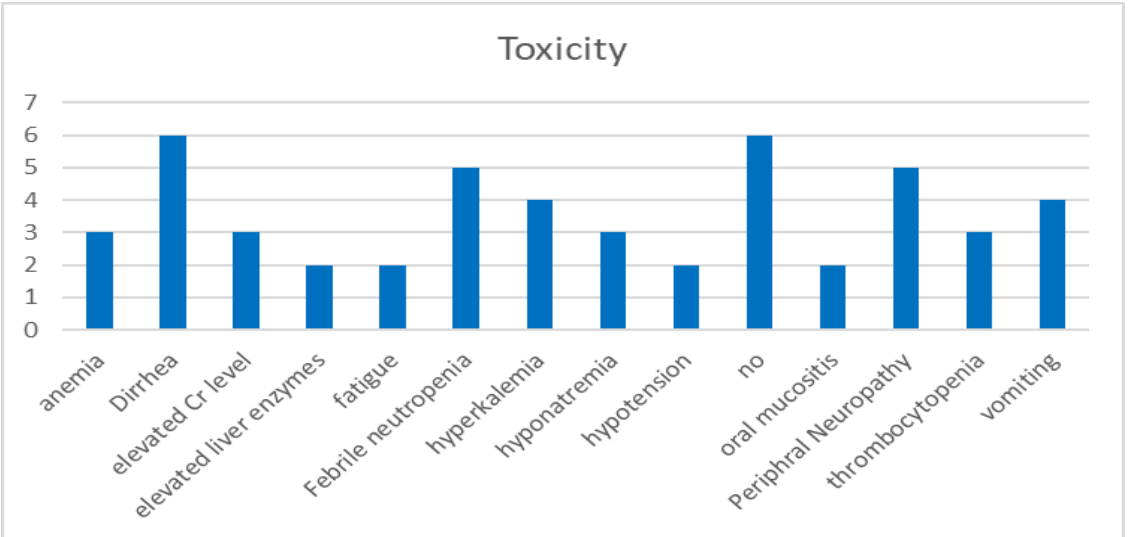

Figure (1): Toxicity (by case) of Modified FOLFIRINOX-losartan.

Table (2): Treatment related toxicity:

Toxicity	No.	%
FOLFIRINOX/losartan		
No toxicity	6	12.0
Yes	44	88.0
Grade		
No toxicity	6	12.0
I	34	68.o
II	7	14.0
III	3	6.0
Toxicity of CCRT		
No	20	40.0
Vomiting	12	24.0
Hand-foot syndrome	8	16.0
Diarrhea	10	20.0
Grade		
No toxicity	20	40.0
I	22	44.0
II	8	16.0

Response was assessed after completion of 3 cycles of modified FOLFIRINOX and losartan. Most of the patients achieved partial response (PR);thirty-two patients (64%), complete response(CR) achieved in nine patients (18%) and nine patients (18%) had stable disease (SD),with no disease progression (DP) to any patients while receiving modified-FOLFIRINOX and losartan (Figure 2). Response was assessed after completion CCRT, Three patients (6%) had CR. Nineteen cases (38%) had PR, while 24 cases (48%) had (SD) and (8%) had PD in the form of local recurrence, peritoneal deposits and liver metastases (Figure 3 and table 3).

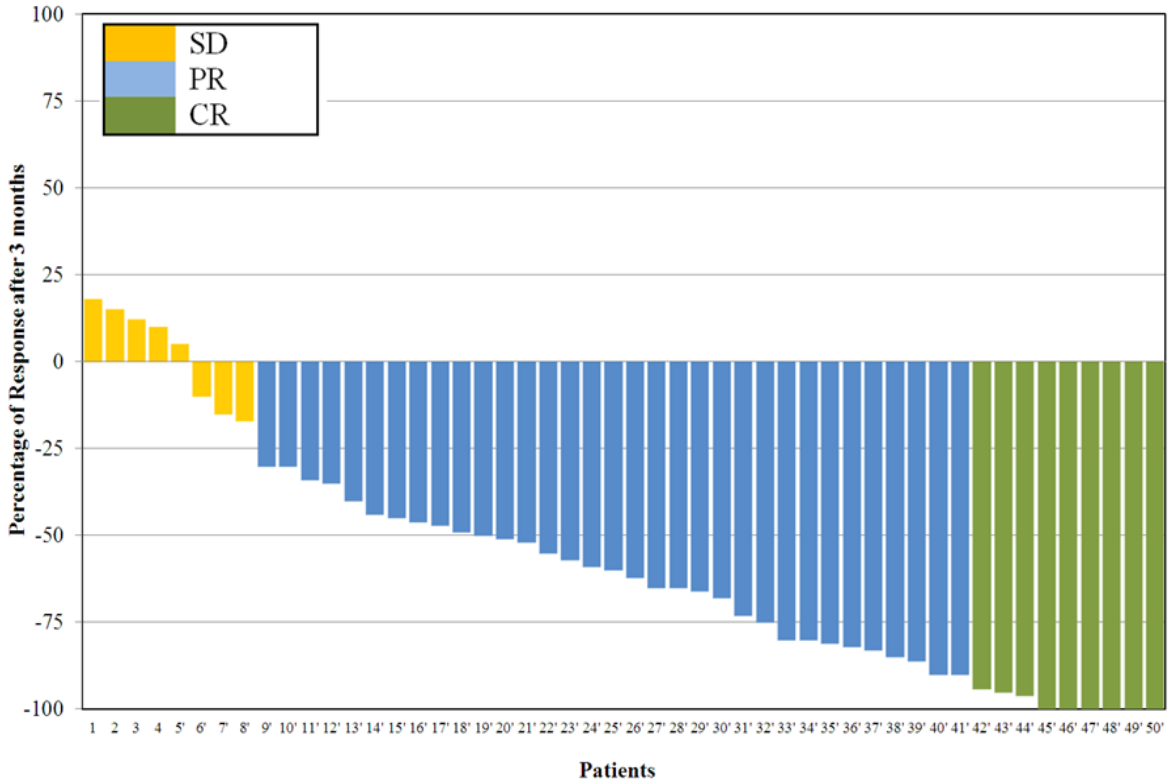

Figure (2): Waterfall Plot of percentage change in tumor dimension after FOLFIRINOX -losartan.

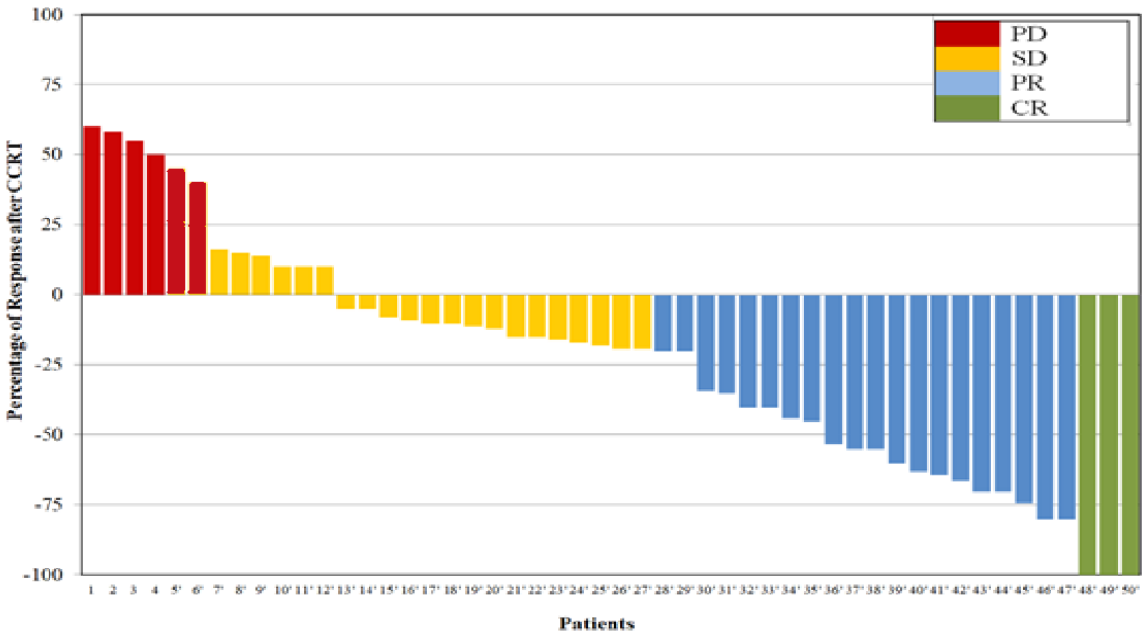

Figure (3): Waterfall Plot of percentage change in tumor dimension after CCRT.

Table (3): Treatment response:

Response	No.	%
FOLFIRINOX/Losartan		
CR	9	18.0
PR	32	64.0
SD	9	18.0
CCRT		
CR	3	6.0
PR	19	38.0
SD	24	48.0
PD	4	8.0

Among the included 50 patients, thirteen patients (26%) underwent resection. R0 margin was achieved in 6 patients (12%), while R1 margin was present in 7 patients (14%). Seven patients (16%) had positive lymph nodes (Table 4).

Table (4): Tumor characteristics regarding surgery (n = 13)

Data		No.	%
Resectability	Resectable	13	26.0
	Irresectable	37	74.0
Margin	R0	6	46.2
	R1	7	53.8
Type of surgery	Whipple operation	10	76. 9
	Distal pancreatectomy	3	23.1
Perineural invasion	Positive	6	46.2
	Negative	7	53.8
Lymphovascular invasion	Negative	6	46.2
	Positive	7	53.8
Nodal involvement	Positive LN	7	53.8
	Negative LN	6	46.2
Tumor size after surgery	Min. – Max.	1.50 – 2.10	
	Mean ± SD.	1.82± 0.18	

There was a statistically significant difference regarding resectability and CEA and response after CCRT. There was no statistically significant difference between resection and patient age, PS, pathological grade, tumor site, tumor size, vascular invasion, CA19.9, toxicity and response after modified FOLFIRINOX-losartan (Table 5).

Table (5): Correlation between tumor and patient characteristics and resectability:

Resectability		Resectable (n = 13)		Irresectable (n = 37)		Test of Sig.	p
		No.	%	No.	%		
Age	Min. – Max. Mean ± SD. Median	23.0 – 60.0 50.77 ± 9.77 54.0		41.0 – 61.0 52.51 ± 5.52 53.0		t=0.792	0.432
Sex	Female Male	4 9	30.8 69.2	13 24	35.1 64.9	χ^2=0.082	^{FE}p= 1.000
ECOG PS	0 1	4 9	30.8 69.2	11 26	29.7 70.3	χ^2=0.005	^{FE}p= 1.000
Tumor site	Head Body and tail	8 5	61.5 38.5	30 7	81.1 18.9	χ^2=2.014	^{FE}p= 0.256
Response of FOLFIRINOX/ losartan.	PR CR SD	7 5 1	53.8 38.5 7.7	25 4 8	67.6 10.8 21.6	χ^2=4.737	^{MC}p 0.102
Response Of CCRT	PR CR SD PD	10 3 0 0	76.9 23.1 0.0 0.0	9 0 24 4	24.3 0.0 64.9 10.8	χ^2=25.058*	**^{MC}p <0.001***
CEA (ng/ml)	Mean ± SD	25.12 ± 6.11		26.16 ± 6.31		χ^2=9.236	**0.013***

SD: Standard deviation t: Student t-test *: Statistically significant at p ≤ 0.05
χ^2: Chi square test MC: Monte Carlo FE: Fisher Exact

After median follow-up duration of 20.25 months (6.0-34.5 months); the median PFS was 12 months (95% CI, 9.647 – 14.353). The patients who had surgical resection had longer median PFS of 12 months (95% CI, (10.552 – 13.448) compared to those who did not have resection; PFS was 10 months (95% CI, 5.963 – 18.037) (P=0.485) (Figure 4). The patients who achieved CR after CCRT had longer PFS (median not reached) compared to those who had PR, SD and PD. Median PFS was 24, 10 and 5 months respectively (95% CI, 13.191 – 34.809), (4.973 – 15.027), and (95% CI, 4.823-5.124). (P=<0.001*) (Figure 5), by univariate analysis, the response after CCRT was the only prognostic factor affecting PFS (Table 6).

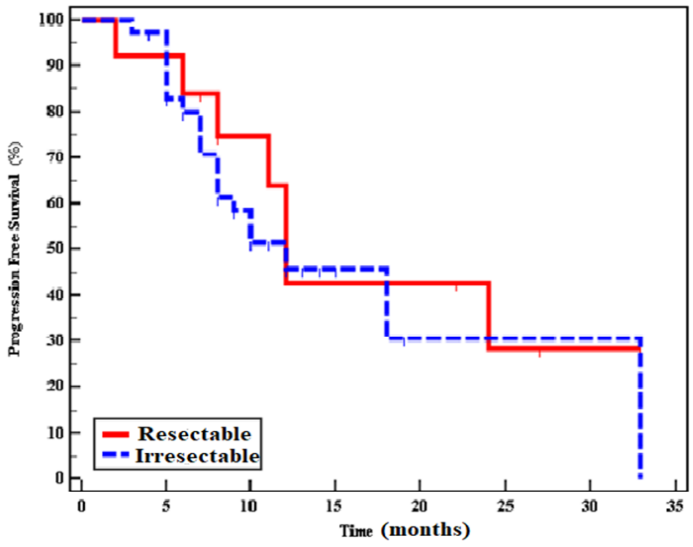

Figure (4): Kaplan-Meier survival curve for PFS with resection (P=0.485).

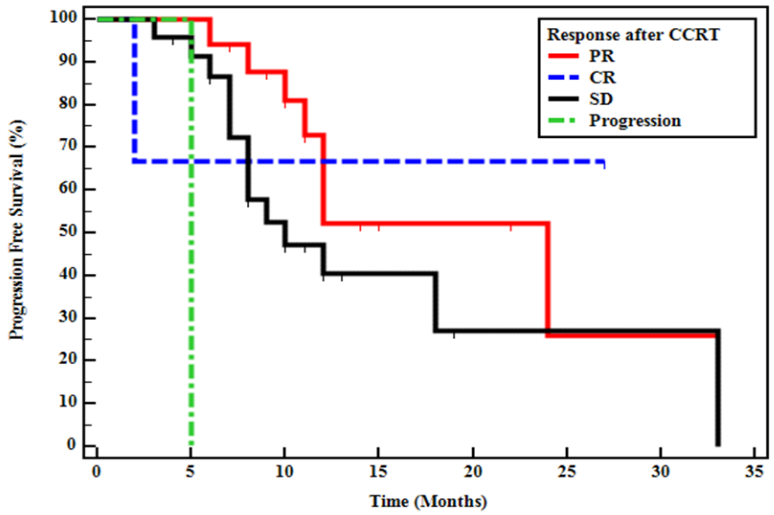

Figure (5): Kaplan-Meier survival curve for PFS with response after CCRT **(P=<0.001*)**.

Table (6): Univariate analysis for the parameters affecting PFS:

Studied data	Univariate			
	Mean PFS (95% CI)	**SE**	**Log-rank**	**P value**
Age according to median <53 ≥53	 22.8(19.5-22.8) 17.1(13.1-25.9)	1.016	2.675	0.555
Gender Female Male	 20(12.4-29.8) 17.6(11.9-26.9)	0.818	1.293	0.631
ECOG PS 0 1	 23.6(20.7-24.9) 22.9(18.9-24.6)	0.977	4.273	0.956
Pathological grade Grade II Grade III	 17.1(10.13-30.14) 14.8(13.74-28.12)	0.721	6.179	0.549
Tumor site Head Body and tail	 15.23(10.86-32.94) 19.53(11.73-29.92)	4.111	1. 772	0.823
Vascular involvement Arterial Venous Both	 16.63(10.23-20.63) 18.3(12.93-22.34) 14.82(9.15-21.92)	1.021	0.466	0.466
Response after CCRT CR PR SD PD	 19.78 (13.590 – 25.972) 18.67 (5.331– 32.003) 15.95 (10.216 – 21.693) 5.0 (5.0 – 5.0)	 2.972 0.463 2.407 1.517	25.190	**<0.001***
Resectability Resectable Irresectable	 17.920 (11.083 – 24.758) 16.830 (11.444 – 22.216)	2.035	0.489	0.485
Margin R0 R1	 12.845(9.623-20.634) 10.934(5.823-16.934)	1.843	2.885	0.874

C.I: Confidence interval *: Statistically significant at $p \leq 0.05$

The median OS was 21 months (95% CI, 10.200–31.800). The patients who had surgical resection had longer OS of 24 months (95% CI, 16.363 – 27.637) compared to those who didn't have resection with median OS was 14 months (95% CI, 9.205 – 18.795) (P=0.271) (Figure 6). The patients who achieved CR after modified FOLFIRINOX had longer OS of 33months (95% CI, 19.918 – 46.082) compared to who had partial response and SD. Median OS was for each 13 months (95% CI, 6.768 – 19.232), (95% CI, 11.718 – 14.282) respectively. By univariate analysis, both the responses after modified FOLFIRINOX-losartan and CCRT were the prognostic factors affecting OS (Table 7).

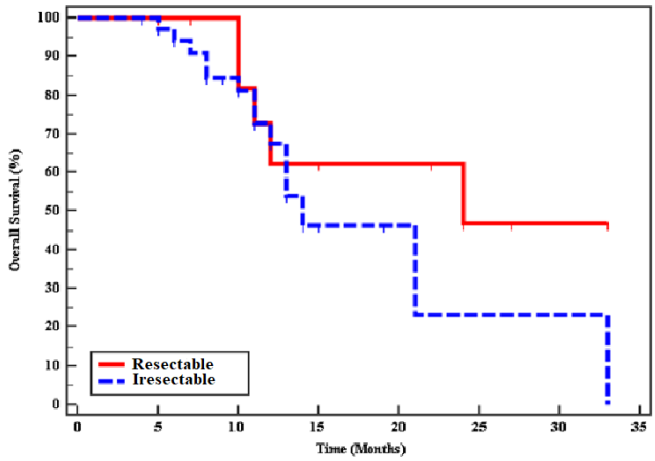

Figure (6): Kaplan-Meier survival curve for OS with resection (P=0.271)

Table (7): Univariate analysis for the parameters affecting OS:

		Mean OS (95% CI)	SE	Log-rank	P value
Age according to median	<53	21.5(19.5-22.8)	1.013	1.677	0.657
	≥53	18.1(13.6-20.7)			
Gender	Female	22(17.4-14.8)	0.859	3.315	0.755
	Male	19.6(15.9-21.9)			
ECOG PS	0	23.6(20.7-24.9)	1.048	2.963	0.924
	1	22.9(18.9-24.6)			
Pathological grade	Grade II	22.1(17.43-23.94)	0.837	2.825	0.779
	Grade III	18.8(15.74-20.72)			
Tumor site	Head	19.53(13.96-30.74)	2.228	0.114	0.114
	Body and tail	21.83(16.92-32.92)			
Vascular involvement	Arterial	16.63(10.23-20.63)	1.49	0.492	0.389
	Venous	18.3(12.93-22.34)			
	Both	14.82(9.15-21.92)			
Response of FOLFIRINOX-losartan	CR	31.20 (26.737 – 35.663)	0.345	6.45	**0.040***
	PR	15.55 (13.030 – 18.063)	1. 639		
	SD	12.8 (11.629 – 14.085)	1.299		
Response after CCRT	CR	27.0 (27.2 – 27.8)	1.78	18.607	**0.001***
	PR	23.03 (16.767– 29.292)	1.96		
	SD	18.0 (11.997 – 24.002)	4.896		
	PD	9.0 (6.470 – 11.530)	2.873		
Resectability	Resectable	23.23(16.911 – 29.557)	3.163	1.21	0.271
	Irresctable	18.27 (12.773 – 23.786)			
Margin	R0	18.2(15.2-19.4)	5.516	0.45	0.45
	R1	15.7(12.8-17.4)			

C.I: Confidence interval; *: Statistically significant at $p \leq 0.05$

By using Cox regression analysis for multivariate analysis of OS, the response after modified FOLFIRINOX-losartan and after CCRT were the independent factors affecting OS (Table 8).The patients who achieved CR after CCRT had longer survival (not reached) compared to those who had PR, SD and PD; median OS was 24, 14 and 8 months respectively (95% CI, 6.761 – 41.239), (95% CI, 11.022 – 16.978), and (95% CI, 4.080 – 11.920) respectively (P=0.001*) (Figures 7 and 8).

Table (8): Multivariate analysis for the parameters affecting OS:

Studied data	Multivariate		
	Mean OS (95%CI)	**P**	**HR (95%C.I)**
Response of FOLFIRINOX-losartan			
CR	29.20 (21.7 – 35.3)	**0.03***	1.826 (1.236-3.936)
PR	14.55 (10.030 – 18.063)		3.013 (3.934-7.567)
SD	10.8 (9.69 – 16.085)		0.469 (0.160-2.521)
Response of CCRT			
CR	26.0 (23.2 – 30.8)	**<0.001***	1.963 (1.634-3.731)
PR	22.03 (12.767– 29.292)		0.532 (0.285-1.963)
SD	16.0 (10.997 – 27.002)		0.345 (0.193-1.834)
PD	7.0 (4.470 – 13.530)		1.834 (1.236-4.623)

HR: Hazard ratio C.I: Confidence interval *: Statistically significant at $p \leq 0.05$
All variables with p<0.05 was included in the multivariate

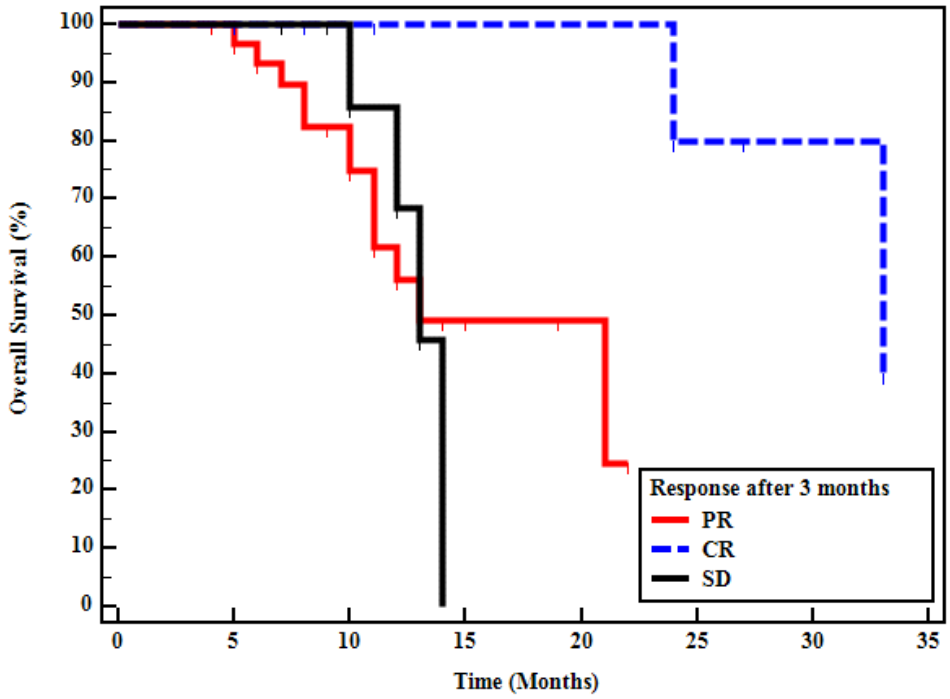

Figure (7): Kaplan-Meier survival curve for OS with response of FOLFIRINOX-losartan **(P=<0. 040*)**.

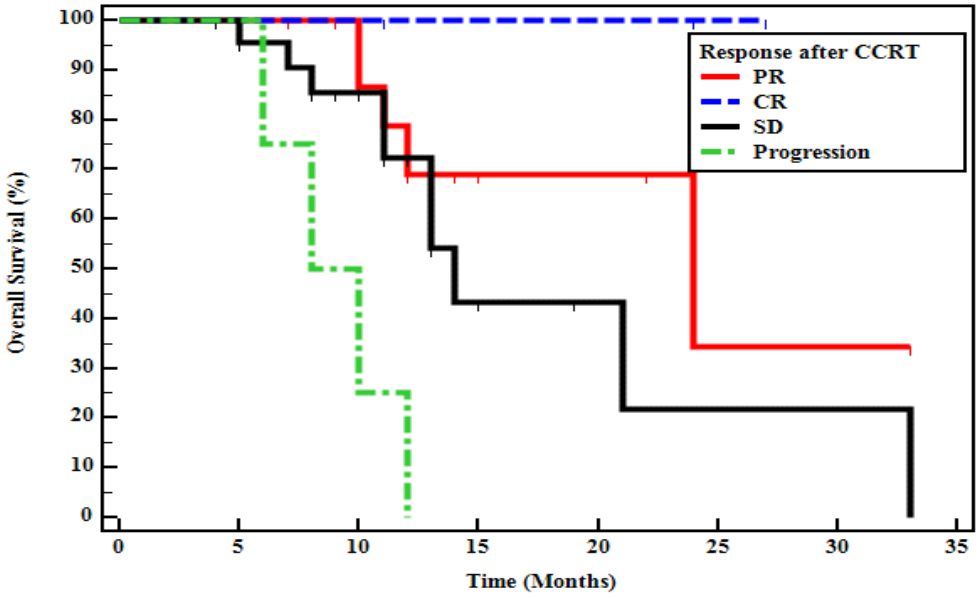

Figure (8): Kaplan-Meier survival curve for OS with response of CCRT **(P=<0.001*)**.

DISCUSSION

The hypothesis that losartan had a role in reducing the oncogenic potential of malignant cells, altering the tumor internal microenvironment and enhancing the delivery of cytotoxic systemic therapy by normalization of the extracellular matrix and activation of immunity, was supported by multiple studies [4].

In this study overall response rate after CCRT was 44%. (6%) of patients had CR. Nineteen cases (38%) had a PR, while 24 patients (48%) had SD and (8%) had PD. **Murphy *et al.*** [2] was one of the earliest studies to evaluate the surgical primary end point in locally advanced PDAC. They investigated 50 patients retrieved over 4 years. They found that only one case achieved a CR by imaging. 23 cases achieved PR, while twenty-one had SD, 2 cases had PD, which is comparable to our results [2].

On the other hand, several trials investigated efficacy of systemic therapy alone in neoadjuvant setting including multiple regimens. **Katz *et al.*** [10] conducted a retrospective analysis, included 129 cases with border-line PDAC who received gemcitabine-based induction chemotherapy followed by CCRT. (69%), (12%), and (19%) of the patients had SD, PR, and DP respectively.

Furthermore, **Stein *et al.*** [11] investigated 31 patients of LAPC received induction chemotherapy modified FOLFIRINOX (4 cycles). (0%), (17.2%), (82.7%), and (0%) of the patients had CR, SD, PR, and DP respectively. Also, **Rombouts *et al.*** [12] analyzed 18 patients received full dose FOLFIRINOX (4 cycled). (0%), (12%), (82%), and (6%) of the patients had CR, PR, SD, and DP respectively.

Maggino *et al.* [13] analyzed 408 LAPC patients who received different induction chemotherapy (FOLFIRINOX-GNP-GEMOX) and (24%) of the patients received CCRT). (30.6%), (31.4%), and (38%) of the patients had PR, SD, and DP respectively. Furthermore, **Ulusakarya *et al.*** [14] investigated 73 patients treated with modified FOLFIRINOX. (8.1%), (35.1%), (35%), and (14%) of the patients had CR, PR, SD, and PD.

In this study, overall response rate was 44% and there were 6 pathologic complete responses; better results than most of the studies investigated neo-adjuvant chemotherapy and compared to (0%) in the borderline analysis reported by **Murphy *et al.*** [2]. The addition of losartan to modified FOLFIRINOX could explain these results.

In the current study, thirteen patients (26%) had surgical resection, agreeing with; **Suker *et al.*** [15] who reported resection rate of 25.9%, in his meta-analysis. On contrast of our results, **Murphy *et al.*** [2] revealed high resectability rate; with (69%) of patients underwent resection, while (31%) remained unresectable. However, it should be taken in consideration the involvement of advanced radiotherapy techniques including MRI guided simulation, SBRT, and proton beam radiotherapy, and the introduction of all patients achieving CR, PR, and SD into surgical exploration.

Most of the studies, which show high resection rates, had heterogeneous spectrum of the patients (resectable, border-line, and locally advanced), this applies on **Kim *et al.*** [16] **and Kharofa *et al.*** [17] with resection rate of (63%) and (70%) respectively, but, on the contrary, **Maggino *et al.*** [13] reported that the resection rate was 15.1%. This could be explained by multiple treatment interruptions (the treatment completion rate was 71.6%).

In this study, the median OS was 21 months (95% CI, (10.200–31.800). In agreement of our results, **Massucco *et al.*** [18] analyzed twenty-eight

cases with LAPC that received induction, gemcitabine based CCRT, the median OS for all the patients was 19 months.

Furthermore, several studies investigated total neoadjuvant protocol using multiple regimens including GEMOX, Gemcitabine-Capcitabine, with median OS of resectable patients was 22, 23.1 (months) vs. 12, 17 (months) for irresectable cases respectively [19-20].

In CONKO-007 trial in which the authors randomized locally advanced patients for induction chemotherapy (gemcitabine or FOLFIRINOX), patients without disease progression were randomized again to either chemotherapy alone or to CCRT; the median overall survival for resectable cases was 26.5 (months), but, for irresectable patients, the median overall survival was 16.5 (months), ($p = 0.003$) [21]. In contrast of our results, multiple studies reported shorted survival outcomes, investigated neo-adjuvant chemotherapy in locally advanced setting.

Philip *et al.* [22] **and Arima *et al.*** [23] investigated FOLFIRINOX and GnP as induction chemotherapy. These studies reported median OS for all cohort 18, and 15 months respectively. Also, the NEOLAP-0113 conducted by **Kunzmann *et al.*** [24] investigated induction chemotherapy (sequential GnP-FOLFIRINOX vs GnP alone), the median overall survival (18.5), (19.3) months for the GnP arm and the sequential arm respectively.

On the other hand, several studies reported longer survival outcomes. **Murphy *et al.*** [2] results showed that the median progression free survival was 17.5 months, while median overall survival was 31.4 months for all cases.

Study limitation: being single arm study with no control arm.

CONCLUSIONS

Modified-FOLFIRINOX/losartan protocol followed by CCRT had high response, feasible and could improve patients' outcomes in LAPC.

- **Conflict of interests:** Authors declare no conflict of interest
- **Funding**: No fund

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