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Neoadjuvant Modified FOLFIRINOX Regimen followed by Stereotactic Body Radiation Therapy (SBRT) in Non-Metastatic Pancreatic Adenocarcinoma

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer, with a 5-year survival of approximately 10%. Most patients present with advanced disease, and only 10–20% have resectable tumors at diagnosis. As surgery remains the only potentially curative treatment, neoadjuvant therapy aims to improve resectability and identify treatment failures early. Multidisciplinary management is essential for borderline resectable and locally advanced PDAC.

Objectives: To evaluate neoadjuvant modified FOLFIRINOX (mFOLFIRINOX) for four months followed by stereotactic body radiotherapy (SBRT) in non-metastatic, borderline resectable and locally advanced pancreatic ductal adenocarcinoma (PDAC), focusing on resectability, progression-free survival (PFS), overall survival (OS), toxicity, and prognostic factors.

Methods: This single-arm prospective phase II trial included 28 patients with non-metastatic, borderline resectable or locally advanced PDAC treated at the National Cancer Institute and Fayoum University from June 2022 to December 2023. Patients received four months of mFOLFIRINOX followed by SBRT. Treatment response, R0 resection, PFS, OS, toxicity, and associations with clinical factors were assessed.

Results: The mean age was 51.3 years (range, 38–69), 67.9% were male, 57.1% were smokers, and 50% had diabetes. Abdominal pain (50%) and jaundice (46.4%) were the most common presenting symptoms, while 64.3% reported weight loss. Only one patient (3.6%) achieved resectability. PFS was significantly longer among non-smokers (p=0.012) and patients with tumors <4 cm (p=0.046). Females had significantly longer OS than males (p=0.017), and non-smokers had better OS than smokers (p=0.029).

Conclusion: In this cohort, mFOLFIRINOX followed by SBRT did not substantially improve resectability or survival in non-metastatic unresectable PDAC. Treatment was associated with considerable toxicity despite supportive care. These findings highlight the need for multidisciplinary management and individualized treatment strategies, particularly in patients with poor treatment tolerance.

Keywords: Pancreatic ductal adenocarcinoma (PDAC) -Modified FOLFIRINOX-SBRT

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the sixth leading cause of cancer-related mortality worldwide, with an increasing incidence projected to rise by 95.4% by 2050. Despite advances in treatment, the global 5-year survival remains approximately 10% [1]. Incidence is highest in developed regions but is also increasing in Asia and Africa, partly due to aging populations and lifestyle changes. PDAC predominantly affects older adults and is associated with modifiable risk factors including smoking, obesity, chronic pancreatitis, diabetes, and excessive alcohol consumption, as well as family history and inherited genetic syndromes. Its insidious onset and nonspecific presentation, commonly including abdominal pain, weight loss, jaundice, and anorexia, frequently result in delayed diagnosis [2].

Surgical resection offers the best chance of cure; however, only 10–20% of patients present with resectable disease, while approximately 35% have locally advanced unresectable disease and 50% present with metastatic disease [3]. Even after resection and adjuvant chemotherapy, 5-year survival remains approximately 20% [4]. Consequently, neoadjuvant multimodality therapy has gained importance, particularly for the 30–40% of patients with borderline resectable or locally advanced PDAC, aiming to control micrometastatic disease, downstage tumors, and increase the likelihood of margin-negative (R0) resection [3, 5].

Several studies support neoadjuvant chemotherapy in borderline resectable and locally advanced PDAC. The ESPAC-5F trial demonstrated improved 1-year survival with preoperative therapy compared with immediate surgery, with the highest survival observed in the FOLFIRINOX arm, although the trial was not designed for direct comparison between treatment regimens [5,6]. A patient-level meta-analysis reported that neoadjuvant FOLFIRINOX achieved a 68% resection rate, with 84% of resections being R0, and median progression-free and overall survival of 18 and 22 months, respectively [7]. Similarly, the Alliance A021101 study demonstrated high rates of pancreatectomy and margin-negative resection following modified FOLFIRINOX-based neoadjuvant therapy [5].

Evidence regarding neoadjuvant chemoradiotherapy remains mixed. PREOPANC-1 did not demonstrate a statistically significant overall survival benefit in the primary analysis, although neoadjuvant treatment improved R0 resection, disease-free survival, distant metastasis-free survival, and locoregional control [8]. The SWOG S1505 trial further demonstrated comparable

resectability and survival outcomes between perioperative modified FOLFIRINOX and gemcitabine/nab-paclitaxel in resectable PDAC [9]. Other studies have reported higher response and pancreatectomy rates with FOLFIRINOX compared with gemcitabine/nab-paclitaxel, although overall survival was similar [10].

The role of radiation therapy in borderline resectable and locally advanced PDAC remains controversial [11]. Stereotactic body radiation therapy (SBRT) has emerged as an alternative radiation technique that delivers highly conformal, ablative doses over a short treatment course. Sequential chemotherapy followed by SBRT has been investigated in borderline resectable PDAC, with reports of increased margin-negative resection and improved survival among patients who ultimately underwent resection, while maintaining relatively low rates of severe toxicity [12].

Given the limited resectability and poor survival associated with borderline resectable and locally advanced PDAC, and the evolving evidence supporting intensive neoadjuvant chemotherapy and SBRT, further evaluation of combined modified FOLFIRINOX followed by SBRT is warranted. This study therefore evaluated the efficacy, resectability, survival outcomes, and toxicity of this sequential approach in patients with non-metastatic PDAC.

PATIENTS AND METHODS

This single-arm prospective phase II clinical trial included patients with newly diagnosed, non-metastatic, unresectable pancreatic ductal adenocarcinoma (PDAC), including borderline resectable and locally advanced disease, treated at the Medical Oncology Department, National Cancer Institute (NCI), Cairo University, and the Oncology Department, Fayoum University Hospital, between June 2022 and December 2023. Eligibility for enrollment was determined by a multidisciplinary gastrointestinal oncology committee.

This single-arm prospective phase II clinical trial included patients with newly diagnosed, non-metastatic, unresectable pancreatic ductal adenocarcinoma (PDAC), including borderline resectable and locally advanced disease, treated at the Medical Oncology Department, National Cancer Institute (NCI), Cairo University, and the Oncology Department, Fayoum University Hospital, between June 2022 and December 2023. Eligibility for enrollment was determined by a multidisciplinary gastrointestinal oncology committee.

Eligible patients were 18–70 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and a life expectancy >6 months, and had adequate cardiac, hepatic, hematologic, and renal function. Cardiac eligibility required an ejection fraction >50%. Hematologic criteria included hemoglobin >10 g/dL, total leukocyte count >4,000/mm³ or absolute neutrophil count >1,200/mm³, and platelet count >150,000/mm³. Hepatic criteria included AST and ALT <3 times the upper limit of normal and total bilirubin <1.2 mg/dL. In patients with biliary obstruction, endoscopic retrograde cholangiopancreatography with biliary stent insertion was permitted. Non-metastatic borderline resectable or locally advanced disease was established by pancreatic-protocol computed tomography according to NCCN criteria (13) and confirmed histologically as PDAC.

Patients with metastatic disease, age <18 or >70 years, inadequate organ function, pathological diagnoses other than adenocarcinoma, previous or synchronous second primary malignancy, or pre-existing peripheral neuropathy were excluded. The study protocol was approved by the Institutional Review Board of the National Cancer Institute. Written informed consent was obtained from all participants before enrollment. Clinical data and tissue samples were coded and de-identified to ensure confidentiality.

TREATMENT AND ASSESSMENT

Patients received four months of induction modified FOLFIRINOX (mFOLFIRINOX), followed by SBRT and, when feasible, surgical resection. Each mFOLFIRINOX cycle was administered every 2 weeks and consisted of oxaliplatin 85 mg/m² intravenously over 2 hours, leucovorin 400 mg/m² intravenously over 2 hours, irinotecan 150 mg/m² intravenously over 90 minutes, and 5-fluorouracil 2400 mg/m² as a continuous intravenous infusion over 46 hours. Dose modifications were performed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Clinical assessment, including performance status and treatment-related toxicity, was performed before each chemotherapy cycle. Complete blood count, liver function tests, and kidney function tests were assessed every 2 weeks. Pancreatic-protocol CT, serum CEA, and CA19-9 were repeated every 8 weeks to assess treatment response and exclude disease progression or newly developed metastases.

Three weeks after completion of chemotherapy, patients underwent contrast-enhanced pancreatic-protocol CT for restaging. Tumor response was assessed according to RECIST criteria [14] by the multidisciplinary committee. Patients with progressive disease received subsequent systemic therapy according to local guidelines and were followed for survival.

Patients without disease progression after chemotherapy received SBRT 4–6 weeks after the last chemotherapy cycle, to a total dose of 30 Gy in five fractions over approximately 1.5 weeks, administered three times weekly with a minimum interval of 48 hours between fractions. Four weeks after completion of SBRT, pancreatic-protocol CT was performed to reassess treatment response according to RECIST criteria [14].

Patients considered suitable for resection underwent surgery 4–6 weeks after completion of SBRT, with the aim of achieving an R0 resection.

Outcomes

The primary endpoints were the R0 resection rate, defined as microscopically tumor-negative surgical margins, and pathological response in the surgical specimen. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and treatment-related toxicity graded according to NCI CTCAE version 5.0.

PFS was defined as the interval from the date of diagnosis to the first documented disease progression, relapse, death, or last follow-up. OS was defined as the interval from the date of diagnosis to death from any cause or the last follow-up.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Quantitative variables were summarized as mean ± standard deviation or median and range, as appropriate, while qualitative variables were presented as frequencies and percentages. Survival distributions were estimated using the Kaplan–Meier method and compared using the log-rank test. All tests were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

Among 28 patients, the mean age was 51.3 years (range, 38–69), with male predominance (67.9%). Diabetes and smoking were present in 50% and 57.1%, respectively. Abdominal pain (50%), jaundice (46.4%), and weight loss (64.3%) were the main presenting features. The mean tumor size was 4.4 cm, with pancreatic head involvement in 78.6%. Vascular involvement was frequent, including arterial, venous, and combined involvement in 75%, 85.7%, and 60.7%, respectively. Median pretreatment CA19-9 was 293.31 U/mL and decreased to 81.85 U/mL after treatment. Endoscopic biopsy was used in 96.4% of patients, while 57.1% required biliary stenting [Table 1].

Treatment duration ranged from 1 to 4 months, with 39.3% completing the planned four months; the remaining patients discontinued treatment mainly because of toxicity or disease progression. Full-dose chemotherapy was administered to 60.7%, while 50% required dose reduction. Treatment delays occurred in 75% of patients, most commonly for one week (46.4%), with 32.1% experiencing one delay and 17.9% experiencing two or more delays [Table 2]. The most frequent adverse events were vomiting (75%), diarrhea (64.3%), fatigue (60.7%), and neutropenia (57.1%), including grade 3 neutropenia in 14.3% of patients [Table 3].

SBRT was administered to 8 patients (28.6%), while 14 (58.3%) developed progressive disease and 2 died following regressive disease from non-disease-related causes [Table 4]. Radiation-related adverse events were generally mild to moderate. Three patients underwent surgery (two explorations and one Whipple

Table 1: Patients characteristics.

Variables	No of patients	%
Age (years): ≤50years	12	42.9
>50years	16	57.1
Sex: Male	19	67.9
Female	9	32.1
BMI: Normal	12	42.9
Overweight	13	46.4
Obese class 1	2	7.1
Obese class 2	1	3.6
Main complaint: Abdominal pain	14	50
Jaundice	13	46.4
Dyspepsia	1	3.6
Weight loss: No	10	35.7
Yes	18	64.3
Diabetes: No	14	50
Yes: Old	11	39.3
Newly diagnosed	3	10.7
Smoking: No	12	42.9
Yes: Mild	3	10.7
Moderate	3	10.7
Severe	10	35.7
Hypertension: No	22	78.6
Yes	6	21.4
Tumor site: Head& uncinate process	22	78.6
Body& neck	6	21.4
Mass correlation: Arterial Only	4	14.3
Venous only	7	25
Arterial & venous	17	60.7
Biopsy method: Endoscopic	27	96.4
Laparoscopic	1	3.6
Stent: No	12	42.9
Yes	16	57.1
Type of stent: Plastic	14	87.5
Metal	2	12.5
Restenting: No	21	75
Yes	7	25

Table 2: Treatment Regimen Variables.

Chemotherapy	Number	Percent
No of months: 1	5	17.90%
2	3	10.70%
3	9	32.10%
4	11	39.30%
No of months: 1-3 months	17	60.70%
4 months	11	39.30%
Full dose: No	11	39.30%
Yes	17	60.70%
Dose reduction: No	14	50%
Yes	14	50%
Delayed: No	7	25%
Yes	21	75%
Delayed frequency: Once	9	32.10%
2 times	5	17.90%
3 times	5	17.90%
4 times	1	3.60%
5 times	1	3.60%
Delayed duration: 1 week	13	46.40%
1-2 weeks	5	17.90%
2-4 weeks	1	3.60%
4 weeks	2	7.10%
SBRT: No	20	71.40%
Yes	8	28.60%

Table 3: Adverse Events of chemotherapy.

Adverse events	All grades	G1	G2	G3
Anorexia	13 (46.4%)	3 (10.7%)	9(32.1%)	1(3.6%)
Nausea	9(32.2%)	4(14.3%)	5(17.9%)	--
Vomiting	21(75%)	11(39.3%)	7(25%)	3(10.7%)
Diarrhea	18 (64.3%)	8(28.6%)	7(25%)	3(10.7%)
Fatigue	17(60.7%)	2(7.1%)	11(39.3%)	4(14.3%)
Hepatotoxicity	6(21.5%)	1(3.6%)	5(17.9%)	--
Neutropenia	16(57.1%)	3(10.7%)	9(32.1%)	4(14.3%)
Peripheral neuritis	18(64.3%)	14 (50%)	4(14.3%)	--
Oral mucositis	3(10.7%)	1(3.6%)	2(7.1%)	--
Anaemia	2(7.2%)	1(3.6%)	1(3.6%)	--
Constipation	2 (7.1%)	--	2(7.1%)	--
Perianal fistula	1 (3.6%)	---	1(3.6%)	
Porta cath infection	1(3.6%)	----	1(3.6%)	

procedure), with only one achieving resection, corresponding to a resectability rate of 3.6% [Table 4]. Post-treatment tumor markers remained elevated in 45.8% of patients for CEA (>5 ng/mL) and 58.3% for CA19-9 (>37 U/mL).

Treatment response was limited. Following chemotherapy, 20.8% achieved a radiological response, 20.8% had stable disease, and 58.3% progressed. After radiotherapy, 37.5% responded, 25% remained stable, and 37.5% progressed. Overall, two thirds of patients (66.7%) had progressive disease as their best response as shown in table [9]. At a median follow up of 9.2 months, the median time to progression was 5.9 months. By the end of follow up, 19 patients (67.9%) had died, 9 patients (32.1%) were alive with the disease, and no patients were lost to follow up. Overall, these findings highlight significant challenges in maintaining treatment schedules and managing toxicities, which may impact patient outcomes and necessitate tailored treatment planning.

The 3-, 6-, and 12-month PFS rates were 71.4%, 28.6%, and 17.1%, respectively, with a median PFS of 4 months [Table 5]. PFS was significantly longer among non-smokers (p=0.012) and patients with tumor size <4 cm (p=0.046). A trend toward longer PFS was observed among overweight/obese patients and those with tumors located in the head or uncinate process, although these associations did not reach statistical significance (p=0.058 and p=0.070, respectively) [Table 5].

Additionally, patients who completed all four months of modified FOLFIRINOX followed by stereotactic body radiation therapy (SBRT), and achieved either stable disease (SD) or responsive disease (RD), demonstrated markedly better PFS outcomes ($p < 0.001$) as shown in [Table 6]. Additionally, patients experiencing fatigue and diarrhea from chemotherapy demonstrated adherence of treatment ($p = 0.061$ and 0.00, respectively).

Table 4: Treatment Outcomes.

Radiotherapy AEs*: No	2	25%
Mild acute AEs	5	62.50%
Moderate acute AEs	1	12.50%
Surgery: No	25	89.30%
Exploration	2	7.10%
Whipple	1	3.60%
Resectability: No	27	96.40%
Yes	1	3.60%
Post CEA: ≤ 5	13	54.20%
> 5	11	45.80%
Post CA19.9: ≤ 37	10	41.70%
>37	14	58.30%
Response post CTH: RD*	5	20.80%
SD*	5	20.80%
PD*	14	58.30%
Response post RT: RD	3	37.50%
SD	2	25%
PD	3	37.50%
Total response: RD	4	16.70%
SD	4	16.70%
PD	16	66.70%
Progression: No	13	46.40%
Local only	4	14.30%
Mets only	1	3.60%
Local & mets	10	35.70%

AEs: adverse events, RD: regressive disease, SD: stationary disease, PD: progressive disease

Table 5: Progression free survival (PFS) and patients' characteristics.

	No.	No of events	PFS at 3 months (%)	PFS at 6 months (%)	PFS at 12 months (%)	Median PFS (months)	p-value
Whole group	28	23	71.40%	28.60%	17.10%	4 months	
Age: ≤ 50	12	10	83.30%	41.70%	12.50%	6 months	
> 50	16	13	62.50%	18.80%	18.80%	4 months	0.509
Sex: Male	19	17	68.40%	21.10%	10.50%	4 months	
Female	9	6	66.70%	44.40%	33.30%	6 months	0.158
Diabetes: No	14	11	71.40%	35.70%	21.40%	4 months	
Yes	14	12	71.40%	21.40%	14.30%	4 months	0.815
Smoking: No	12	8	83.30%	58.30%	33.30%	7 months	
Yes	16	15	62.50%	6.30%	--	4 months	0.012
Hypertension: No	22	19	68.20%	22.70%	12.10%	4 months	
Yes	6	4	83.30%	50%	33.30%	6 months	0.222
Weight loss: No	10	8	40%	30%	20%	2 months	
Yes	18	15	88.90%	27.80%	16.70%	5 months	0.572
BMI: Normal	12	11	58.30%	8.30%	8.30%	4 months	
Overweight, obese	16	12	81.30%	43.80%	25%	6 months	0.058
Jaundice: No	12	10	75%	25%	16.70%	4 months	
Yes	16	13	68.80%	31.30%	18.80%	5 months	0.633
Stent: No	12	10	75%	25%	16.70%	4 months	
Yes	16	13	68.80%	31.30%	18.80%	5 months	0.633
Restenting: No	21	17	71.40%	23.80%	19%	4 months	
Yes	7	6	71.40%	28.60%	14.30%	5 months	0.85
Tumor size: < 4 cm	9	6	88.90%	44.40%	33.30%	6 months	
≥4 cm	19	17	63.20%	21.10%	10.50%	4 months	0.046
Tumor site:							
Head & uncinate process	22	20	68.20%	18.20%	9.10%	4 months	
Body & neck	6	3	83.30%	66.70%	50%	9 months	0.07
Arterial correlation:							

No	7	7	42.90%	14.30%	0%	3 months	
Yes	21	16	81%	33.30%	22.90%	5 months	0.041
Venous correlation:							
No	4	4	75%	25%	0%	3.5 months	0.448
Yes	24	19	70.80%	29.20%	20.80%	4 months	
Mass correlation:							
Arterial Only	4	4	50%	25%	0%	3.5 months	
Venous only	7	7	42.90%	14.30%	0%	3 months	0.067
Arterial & venous	17	12	82.40%	35.30%	29.40%	6 months	
Pretreatment CEA:							
≤ 5	13	9	69.20%	46.20%	30.80%	5 months	0.152
> 5	15	14	73.30%	13.30%	6.70%	4 months	
Pretreatment CA19.9							
≤ 37	8	7	50%	25%	12.50%	3 months	
> 37	20	16	80%	30%	18.80%	5 months	0.368
Alkaline phosphatase:							
Normal	15	13	66.70%	20%	13.30%	4 months	
Raised	13	10	76.90%	38.50%	23.10%	6 months	0.213

Table 6: Progression free survival (PFS) and treatment variables.

	No.	No of events	PFS at 3 months (%)	PFS at 6 months (%)	PFS at 12 months (%)	Median PFS (months)	p-value
Number of months:							
1-3 months	17	17	52.90%	0%	0%	3.5 months	**<0.001**
4 months	11	6	100%	72.70%	43.60%	12 months	
Full dose: No	11	8	72.70%	45.50%	27.30%	6 months	
Yes	17	15	70.60%	17.60%	11.80%	4 months	0.143
Dose reduction: No	14	12	71.40%	21.40%	14.30%	4 months	
Yes	14	11	71.40%	35.70%	21.40%	5 months	0.33
Delayed months: No	7	5	57.10%	28.60%	28.60%	3.5 months	
Yes	21	18	76.20%	28.60%	12.70%	5 months	0.858
Anorexia: No	15	11	60%	40%	25%	4 months	
Yes	13	12	84.60%	15.40%	7.70%	5 months	0.469
Nausea: No	19	14	63.20%	31.60%	25.30%	4 months	
Yes	9	9	88.90%	22.20%	0%	5 months	0.497
Vomiting: No	7	7	71.40%	14.30%	0%	4 months	
Yes	21	16	71.40%	33.30%	23.80%	4 months	0.3
Diarrhea: No	10	6	80%	40%	40%	6 months	
Yes	18	17	66.70%	22.20%	5.60%	4 months	0.06
Fatigue: No	11	8	90.90%	45.50%	27.30%	6 months	
Yes	17	15	58.50%	17.60%	11.80%	3.5 months	0.061
Hepatotoxicity: No	22	17	72.70%	27.30%	22.70%	4 months	
Yes	6	6	66.70%	33.30%	0%	3.5 months	0.416
Neutropenia:							
No	12	10	58.30%	25%	16.70%	4 months	0.699
Yes	16	13	813.00%	31.30%	16.70%	4 months	
Peripheral neuritis:							
No	10	7	50%	40%	26.70%	2 months	0.625
Yes	18	16	83.30%	22.20%	11.10%	4 months	

Furthermore, patients with post-chemotherapy carcinoembryonic antigen (CEA) levels below 5 also showed significantly improved PFS (p = 0.007) as shown in [Table 7].

During the study period, 19 patients died. Median follow-up was 8 months (range, 2–19 months), and median OS was 8 months. The cumulative OS rates were 67.9% at 6 months, 33.4% at 12 months, and 28.6% at the end of follow-up [Table 8].

Female patients had significantly longer OS than males (p=0.017), while non-smokers had better OS than smokers (p=0.029). Patients with tumors involving the body and neck had longer OS than those with tumors in the head and uncinate process (p=0.042); however, this finding should be interpreted cautiously because only 6 patients had tumors in the body/neck [Table 13]. Completion of four months of chemotherapy was also associated

Table 7: Progression free survival (PFS) and post treatment variables.

	No.	No of events	PFS at 3 months (%)	PFS at 6 months (%)	PFS at 12 months (%)	Median PFS (months)	p-value
Post chemotherapy CEA: ≤ 5							
> 5	13	8	76.90%	53.80%	36.90%	7 months	
	11	11	81.80%	9.10%	0%	4 months	**0.007**
Post chemotherapy							
CA19.9: ≤ 37	10	7	80%	50%	30%	6 months	
> 37	14	12	78.60%	21.40%	14.30%	4 months	0.205
Resectability: No	27	23	70.40%	25.90%	13.90%	--	No p value
Yes	1	0	--	--	--	--	
Response post chemotherapy+SBRT							
RD+SD							
PD	10	5	100%	80%	48%	12 months	<0.001
	14	14	64.30%	0%	0%	3.5 months	
Response post SBRT:							
RD	3	0			100%		No p value
SD	2	0			100%		
PD	3	3			33.30%		

Table 8: Overall survival and patients characteristics.

	No.	No of events	Cumulative survival at 6 months (%)	Cumulative survival at 12 months (%)	Median survival (months)	p-value
Whole group	28	19	67.90%	33.40%	8 months	
Age: ≤ 50	12	8	83.30%	37.50%	11 months	
> 50	16	11	56.30%	31.30%	7 months	0.467
Sex: Male	19	16	57.90%	21.10%	7 months	
Female	9	3	88.90%	59.30%	Not reached	0.017
Diabetes: No	14	9	57.10%	41.70%	9 months	
Yes	14	10	78.60%	24.10%	8 months	0.763
Smoking: No	12	6	83.30%	55.60%	13 months	0.029
Yes	16	13	56.30%	18.80%	6.5 months	
Hypertension: No	22	15	63.60%	33.50%	8 months	
Yes	6	4	83.30%	33.30%	8 months	0.687
Weight loss: No	10	7	70%	30%	8 months	
Yes	18	12	66.70%	36.70%	8 months	0.961
BMI: Normal	12	9	58.30%	25%	6.5 months	
Overweight, obese	16	10	75%	40.90%	11 months	0.22
Jaundice: No	12	6	83.30%	54%	13 months	
Yes	16	13	56.30%	18.80%	6.5 months	0.066
Stent: No	12	6	83.30%	54%	13 months	
Yes	16	13	56.30%	18.80%	6.5 months	0.066
Re-stenting: No	21	13	71.40%	40.40%	8 months	
Yes	7	6	57.10%	14.30%	7 months	0.3
Tumor size:						
< 4 cm	9	4	77.80%	48.60%	12 months	0.164
≥ 4 cm	19	15	63.20%	26.30%	8 months	
Tumor site:						
Head & uncinate process	22	17	63.30%	17.90%	8 months	
Body & neck						0.042
	6	2	83.30%	83.30%	Not reached	
Arterial correlation: No						
Yes	7	6	42.90%	14.30%	6 months	0.104
	21	13	76.20%	39.70%	11 months	
Venous						
correlation: No	4	3	100%	25%	11 months	0.624
Yes	24	16	62.50%	36.10%	8 months	

Pretreatment						
CEA: ≤ 5	13	7	76.90%	46.20%	12 months	0.079
> 5	15	12	60%	20.30%	8 months	
Pretreatment CA19.9: ≤ 37						
> 37	8	6	50%	37.50%	6 months	0.394
	20	13	75%	32.30%	8 months	
Alkaline phosphatase:						
Normal						
Raised	15	9	73.30%	43.20%	11 months	0.41
	13	10	61.50%	23.10%	8 months	

Table 9: Overall survival and treatment variables.

	No.	No of events	Cumulative survival at 6 months (%)	Cumulative survival at 12 months (%)	Median survival (months)	p-value
Number of months:						
1-3 months	17	14	52.90%	15.70%	6.5 months	0.012
4 months	11	5	90.90%	60.60%	13 months	
Full dose: No	11	6	81.80%	36.80%	11 months	
Yes	17	13	58.80%	29.40%	7 months	0.224
Dose reduction:						
No	14	10	71.40%	35.70%	8 months	0.855
Yes	14	9	64.30%	28.90%	9 months	
Delayed months:						
No	7	4	71.40%	42.90%	8 months	0.649
Yes	21	15	66.70%	29.50%	8 months	
Anorexia: No	15	9	66.70%	45%	12 months	
Yes	13	10	69.20%	17.90%	8 months	0.262
Nausea: No	19	11	68.40%	40.20%	8 months	
Yes	9	8	66.70%	16.70%	8 months	0.256
Vomiting:						
No	7	7	28.60%	0%	5 months	0.007
Yes	21	12	81%	45.40%	11 months	
Diarrhea: No	10	5	80%	45.70%	11 months	
Yes	18	14	61.10%	26.70%	7 months	0.147
Fatigue: No	11	6	63.60%	50.90%	13 months	
Yes	17	13	70.60%	23.50%	8 months	0.376
Hepatotoxicity: No	22	14	68.20%	39.40%	8 months	
Yes	6	5	66.70%	16.70%	9 months	0.774
Neutropenia: No	12	9	66.70%	25%	7 months	
Yes	16	10	68.80%	39.30%	11 months	0.361
Peripheral neuritis:						
No	10	7	50%	30%	4 months	0.685
Yes	18	12	77.80%	36.40%	8 months	

Table 10: Overall survival and post treatment variables.

	No.	No of events	Cumulative survival at 6 months (%)	Cumulative survival at 12 months (%)	Median survival (months)	p-value
Post chemotherapy CEA: ≤ 5						
> 5	13	7	84.60%	46.20%	12months	
	11	8	72.70%	27.70%	8 months	0.285
Post chemotherapy						
CA19.9:						
≤ 37	10	6	80%	48%	12months	0.824
> 37	14	9	78.60%	31.40%	8 months	
Chemotherapy followed by SBRT:						
No						
Yes	20	16	55%	15%	6.5months	0.004
	8	3	100%	75%	Not reached	
Response post chemotherapy:						

RD						
SD	5	2	100%	60%	Not reached	
PD	5	3	80%	60%	13 months	0.248
	14	10	71.40%	21.40%	8 months	
Response post chemotherapy:						
RD+SD						
PD	10	5	90%	60%	13 months	0.106
	14	10	71.40%	21.40%	8 months	
Response post SBRT: RD						
SD	3	0	100%	100%	--	No p value
PD	2	0	100%	100%	--	
	3	3	100%	33.30%	--	

with longer OS (p=0.012). Patients who received chemotherapy followed by SBRT had significantly longer OS (p=0.004) [Table 8-10].

DISCUSSION

In our cohort of 28 patients with non metastatic unresectable PDAC, the primary endpoint of resectability was not achieved with only one patient (3.6%) undergoing curative surgery which is lower than other trials as LAPC-1 (multicenter phase II included 50 LAPC patients) trial which has 6 patients (12%) had resection , all are complete resection R0 [15] also another USA retrospective study was conducting using the National Cancer Data Base (NCBD) which included 5828 non-metastatic pancreatic adenocarcinoma, showed 84.9% Ro in chemo+SBRT arm which was statically significant versus neoadjuvant chemotherapy alone and not statically significant versus chemo+CFRT and it was associated with higher rate of T stage downstaging and N stage downstaging than chemo-CFRT(both p<0.001) [16]. Colorado Cancer Center retrospective study which included 103 (85 BRPC and 18 LAPC) patients, showed 71% of patients had definitive surgery with 97% of them had Ro resection in response to neoadjuvant chemotherapy followed by SBRT [17]. ALLIANCE A021501 (prospective phase II of 126 BRPC patients) trial showed that Resection rate was (33% Ro in mFOLFIRINOX+ RTH versus 57% in mFOLFIRINOX alone) for BRPC [18]. Another Korean retrospective study (50 LAPC patients) showed Resectability rate 18% (9 patients 10% R0 resection in LAPC, also it found that higher radiation dose (>= 35 Gy) is associated higher rate of conversion surgery (25% (8/32) Vs 5.6% (1/18) respectively (19). A (Tran Atlantic Pancreatic Surgery) TAPS Consortium Study which included 531 BRPC neoadjuvant m FOLFIRINOX followed by RTH, showed lower resection rate in RTH arm in BRPC received m FOLFIRINOX followed by RTH (55.3% versus 72.7% p=0.002) with more statically significant node negative disease (57.3% vs 37.6% p=0.01) and major pathological response < 5% tumor viability (24.7% vs 8.3% p=0.006) [7]. In Polish prospective single arm study included 30 LAPC patients, the resection rate was only 3 patients (10%) which didn't reach expected resection 30% [20].

In our study, Median Progression Free survival (PFS) was 4 months, and 1-year PFS was 17.1% which is lower than other trials like LAPC- 1 trial which was 9 months and 34%, respectively [15], Korean retrospective institutional study median PFS was 16.7 months [19], while in the Polish Prospective single arm study median PFS was 7.53 months [20].

Despite poor PFS our data revealed prognostic patterns consistent with international experience. There was a statistically significant improvement in progression-free survival (PFS) among non-smokers (p = 0.012) which is consistent with that smoking is major risk factor of PDAC (20) and smoking cessation is essential for treatment and also patients with tumor sizes less than 4 cm (p = 0.046) also as shown in the Korean study where smaller tumors (<2.9cm) (p=0.048) and also high total dose of SBRT(=>35Gy) (p = 0.011) had statically significant favorable prognosis [19] unlike our study in which we gave 30 Gy. Additionally, patients who completed all four months of modified FOLFIRINOX followed by stereotactic body radiation therapy (SBRT), and achieved either stable disease (SD) or responsive disease (RD), demonstrated markedly better PFS outcomes (p < 0.001). which is correlated with trials showing full neoadjuvant mFOLFIRINOX (4-8 months) had better effect on survival and SBRT has local control effect. Furthermore, patients with post-chemotherapy carcinoembryonic antigen (CEA) levels below 5 also showed significantly improved PFS (p = 0.007).

Overall Survival (OS) in our study median OS was 8 months, and 1 year OS was 33.4%, which is lower than several studies like, LAPC-1 trial which was 15 months and 64% respectively (15) while in USA retrospective study median OS was 32.1 months vs 27.1 months for chemo/SBRT vs Chemotherapy respectively (16), also A TAPS consortium study median OS was 26.2 months with RTH compared with 32.8 months without RTH but was not statically significant (p=0.71) also there was similar survival benefit between SBRT and conventional RTH for BRPC [7]. ALLIANCE A021501 trial median OS was 17.1 months vs 29.8 months in RTH arm vs m FOLFIRINOX alone respectively [18]. The Korean retrospective study, median OS was 26.3 months [19] and in the Polish prospective trial median OS was 13.87 months and 1 year OS was 63.3% (20). Unlike the TAPS Consortium study which showed no significant difference in OS after adding RTH to neoadjuvant mFOLFIRINOX [7]. Also, another Korean study included 212 BRPC showed adding RTH to neoadjuvant chemotherapy significantly increase 2 years OS (82.6% vs 73% , p=0.008) , better local control with preference of surgery within 4 weeks following RTH as it enhances perioperative outcomes [21].

Treatment-related factors were also found to significantly influence overall survival. Patients who successfully completed four months of chemotherapy demonstrated improved OS compared to those who did not ($p = 0.012$). Furthermore, patients who received chemotherapy followed by stereotactic body radiotherapy (SBRT) achieved significantly better survival outcomes ($p = 0.004$) which coincides with USA NCDB based trial which shows chemo / SBRT arm significant OS ($p < 0.05$) especially in patients with T3-4 and node positive disease

Future randomized trials, such as STEREOPAC (randomized comparative ongoing multicenter Phase II trial), are designed to definitively test whether isotoxic high dose SBRT combined with chemotherapy (m FOLFIRINOX or Gemcitabine Nab paclitaxel) improves disease free survival and R0 resection rates compared with chemotherapy alone [22]. Until such data mature, the accumulating retrospective and prospective evidence suggests that chemo SBRT is a promising strategy for patients with borderline resectable and locally advanced PDAC, particularly when systemic therapy is completed and SBRT is delivered at sufficient dose intensity.

Adverse events were frequent: vomiting (75%), diarrhea (64.3%), and fatigue (60.7%) were the most common, with grade 3 toxicities observed in a subset. Neutropenia occurred in 57.1% of patients, including 14.3% with grade 3 severity while in the Polish prospective trial overall 11 grade >=3 adverse events were noted [20].

The disparity between the 3.6% conversion rate in our study and the superior rates reported in international literature can be attributed to several clinical, anatomical, and structural variables. Unlike the Colorado study or the Alliance trial-which heavily featured borderline resectable patients who possess an inherently higher baseline surgical clearance potential-our cohort consisted entirely of strictly unresectable disease at presentation. Transitioning from an unresectable state to a surgical state represents a much more complex biological and anatomical challenge than upgrading a borderline case to a clean resection. Furthermore, SBRT induces dense local fibrosis and scar tissue around the primary tumor and major mesenteric vasculature. On post-treatment CT scans, this dense fibrosis looks radiographically identical to a viable, active tumor. In studies like the Polish trial, the protocol dictated routine surgical exploration for patients who demonstrated stable, non-progressive disease. In our cohort, a strict reliance on post-treatment imaging criteria likely led to a false-positive assessment of persistent unresectability, thereby denying patients exploratory surgeries where the tumor might have already been sterilized.

Additionally, our cohort represents a real-world, selected patient population was small sample size (n = 28) as during recruiting patients most of them had performance status >1, which indicate disease aggressiveness and late discovery making it so hard to collect large number of patients. In real-world practice, patients frequently experience chemotherapy dose reductions, delays, or interruptions due to cumulative mFOLFIRINOX toxicities (such as profound neutropenia or gastrointestinal distress), reducing local downstaging power. Finally, the efficacy of vascular clearance following SBRT is heavily dose-dependent. Dose of SBRT was low in comparison with significant dose affecting local control, resectability and survival in trials (30 Gy versus >= 35Gy) as corroborated by the findings of Jung et al. [19].

Consequently, the low conversion rate (3.6%) observed in this study underscores the inherent limitations of relying solely on traditional radiographic reassessment following the mFOLFIRINOX and SBRT sequence in true LAPC patients. Future protocols should consider adopting routine surgical exploration for patients maintaining stable systemic disease, as imaging frequently overestimates residual vascular involvement due to radiation-induced fibrosis. Furthermore, maximizing the biologically effective dose of SBRT, where clinically safe, remains a crucial parameter to optimize local downstaging.

Clinical Implications

Modified FOLFIRINOX followed by SBRT showed limited overall resectability and survival in unresectable PDAC, with substantial treatment-related toxicity. Patients who completed chemotherapy and proceeded to SBRT had better survival outcomes, emphasizing careful patient selection and multidisciplinary management.

Strengths

The study had a prospective phase II design, predefined eligibility and treatment protocols, multidisciplinary assessment, standardized response and toxicity evaluation, and complete follow-up of all enrolled patients.

LIMITATIONS

The main limitations were the small sample size (n=28), single-arm design, absence of a control group, frequent treatment delays and dose modifications, low proportion receiving SBRT, and short follow-up. Post-SBRT fibrosis may also have complicated radiological assessment of resectability.

CONCLUSIONS

Non-metastatic unresectable PDAC remains a highly lethal disease, with delayed presentation representing a major clinical challenge. In this cohort, sequential mFOLFIRINOX followed by SBRT did not substantially improve resectability or survival and was associated with considerable treatment-related toxicity despite supportive care. Multidisciplinary evaluation and individualized treatment selection are therefore essential. More precise assessment of tumor–vascular relationships may help identify patients most likely to benefit from neoadjuvant therapy and achieve surgical resection.

ETHICAL CONSIDERATIONS

The study was reviewed and approved by the Institutional Review Board of the National Cancer Institute, Cairo University. The study was conducted in accordance with the ethical principles governing research involving human participants. Written informed consent was obtained from all participants before enrollment in the study. Clinical information and tissue samples were coded and de-identified to ensure participants' privacy and confidentiality.

INFORMED CONSENT

Written informed consent was obtained from all participants prior to enrollment in the study and before the initiation of study-related procedures.

CONFIDENTIALITY OF DATA

The confidentiality and privacy of all study participants were maintained throughout the study. Clinical data and tissue samples were coded and de-identified, and no personally identifiable information was disclosed in the manuscript. Study data were handled in accordance with institutional requirements for the protection of participants' confidentiality.

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AUTHOR CONTRIBUTIONS

Maha Alaa El Din Abd El Fatah: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

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Fouad Abd El Shahed Fouad: Investigation, Resources, Validation, Writing – Review & Editing.

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All authors read and approved the final version of the manuscript and agreed to be accountable for the work.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

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