Ann Surg Oncol
DOI 10.1245/s10434-015-4647-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

FOLFIRINOX Induction Therapy for Stage 3 Pancreatic Adenocarcinoma

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ABSTRACT

Background. Reports show that FOLFIRINOX therapy for pancreatic ductal adenocarcinoma (PDAC) results in objective response rates two to threefold higher than those of other regimens. This study aimed to assess response and resection rates for locally unresectable (stage 3) patients initially treated with induction FOLFIRINOX.

Methods. The institutional cancer database was queried for patients treated with induction FOLFIRINOX therapy between 2010 and 2013. Patients were included in the study if they were treated at the authors' institution for stage 3 PDAC (locally unresectable) that had been adjudicated at a weekly multidisciplinary tumor board.

Results. The study identified 101 patients. The median age was 64 years (range 37–81 years), and the median follow-up period was 12 months (range 3–37 months). The patients received a median of six cycles (range 1–20 cycles) of induction FOLFIRINOX. No grade 4 or 5 toxicity was recorded. At the initial restaging (median of 3 months after diagnosis), 23 patients (23 %) had developed distant metastases, 15 patients (15 %) had undergone resection, and 63 patients (63 %) had proceeded to chemoradiation. In the group of 63 patients who had proceeded to chemoradiation (median of 9 months after diagnosis), an additional 16 patients (16 %) had undergone resection, and 5 patients (5 %) had developed metastases. A partial radiographic response was observed in 29 % of all the patients, which was associated with ability to perform resection ($p = 0.004$). The median overall survival time was 11 months for the group that progressed with FOLFIRINOX and 26 months for the group that did not progress.

Conclusion. Nearly one third of the patients who had been initially identified as having stage 3 pancreatic carcinoma and had been treated with FOLFIRINOX responded radiographically and underwent tumor resection.

A recently completed phase 3 randomized trial for stage 4 pancreatic ductal adenocarcinoma (PDAC) identified FOLFIRINOX as superior to gemcitabine in terms of radiographic response together with improved progression-free and overall survival.[1] Patients who received FOLFIRINOX experienced a 32 % objective response rate (ORR) compared with 9 % in the gemcitabine arm of the study, which correlated with survival benefit (median overall and progression-free survival, 11 and 6 versus 7 and 3 months, respectively).

Retrospective studies of patients with both borderline resectable PDAC (stages 1 and 2) and stage 3 disease (locally unresectable) also have suggested an ORR of approximately 30 % with FOLFIRINOX.[2,3] The reported ORR from non-FOLFIRINOX regimens has generally been in the range of 10 %, including the results of a phase 2

This study was presented at the American College of Surgeons Annual Clinical Congress, October 26–30, 2014, San Francisco.

Electronic supplementary material The online version of this article (doi:10.1245/s10434-015-4647-4) contains supplementary material, which is available to authorized users.

First Received: 3 February 2015

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Published online: 12 June 2015

study from our institution that demonstrated a 10 % ORR for resectable patients treated with preoperative gemcitabine and oxaliplatin therapy.[4]

Conversion from unresectable to resectable disease using induction therapy is an important therapeutic goal for stage 3 patients, with studies suggesting its association with improved survival.[5] During the pre-FOLFIRINOX era, the conversion rates for stage 3 patients using induction therapy ranged between 7 and 19 %.[6–13] Currently, the resectability rates after induction FOLFIRINOX for stage 3 PDAC are not established because recent series assessing FOLFIRINOX for non-metastatic patients have been either single-arm surgical series with a denominator limited to selected patients taken to the operating room or series composed of a heterogonous population that included both resectable and locally unresectable patients.[14]

The current study design attempted to overcome these limitations by identifying all stage 3 PDAC patients treated with induction FOLFIRINOX therapy at our institution, whether their tumor was resected or not. This report presents a comprehensive evaluation of FOLFIRINOX induction therapy for all patients who presented with stage 3 PDAC (locally unresectable) and were treated with induction FOLFIRINOX therapy at our institution between 2010 and 2013. The primary aim of this study was to evaluate the radiographic response and resection rates after induction therapy with FOLFIRINOX.

METHODS

Study Design

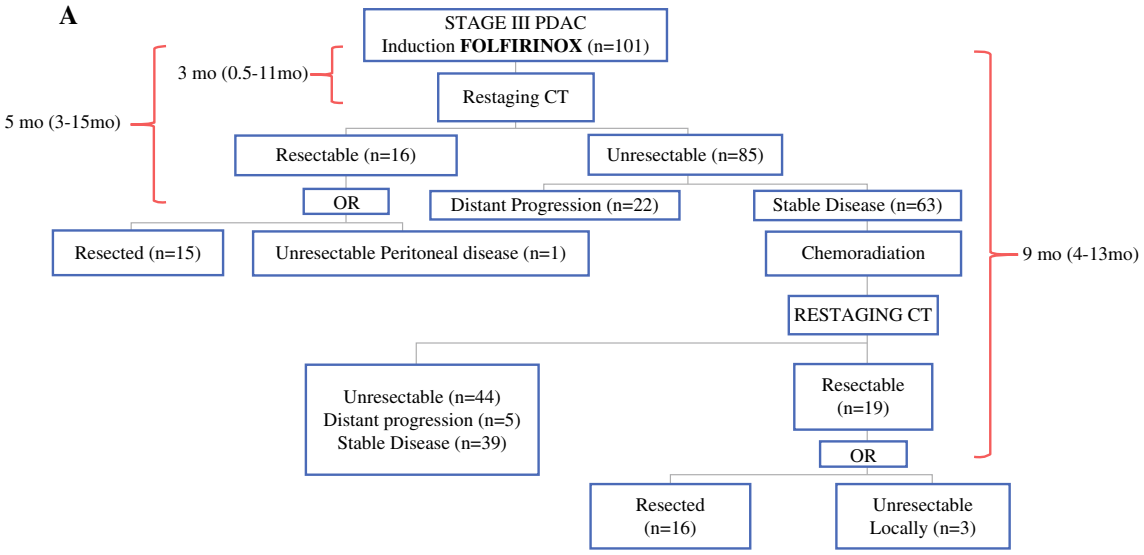
The study was approved by the Institutional Review Board. A search of our institutional cancer database for patients who initially presented with stage 3 PDAC and then were treated with induction FOLFIRINOX therapy was performed. This search identified 106 patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) between 2010 and 2013. Five patients were excluded from the study by chart review. Three of these patients were considered borderline resectable (encasement of the portal vein accompanied by marked lymphadenopathy), and the remaining two patients were excluded because subsequent biopsy identified extra-regional nodal involvement. Treatment-related variables were obtained from the database and confirmed by chart review.

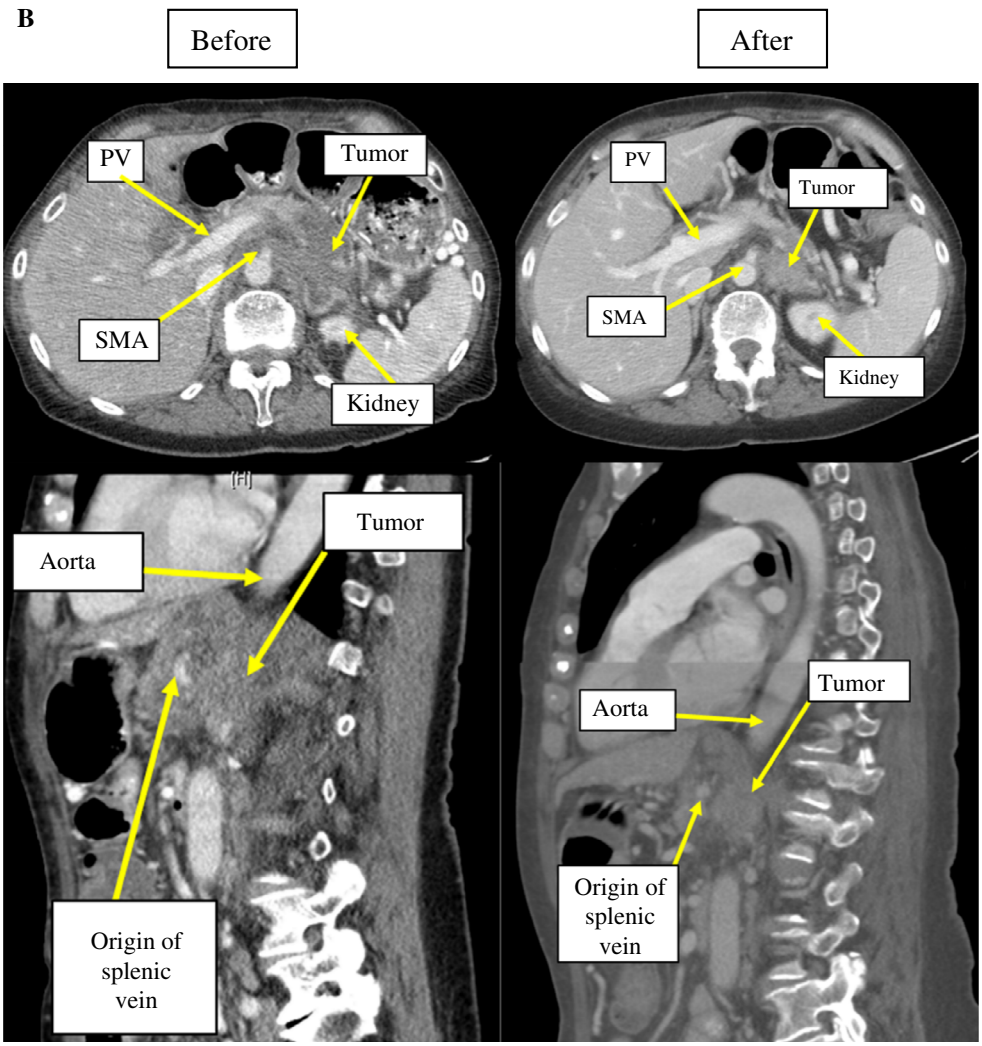
The classification of stage 3 disease was defined according to the National Comprehensive Cancer Network definitions.[15] Only patients categorized as T4, any N, M0 were included in the study. No patients had extra-regional metastatic disease. Further descriptions of findings consistent with local unresectability included the following: superior mesenteric artery encasement greater than 180°, any celiac abutment, inferior vena cava, unreconstructable superior mesenteric vein/portal occlusion, and aortic invasion or encasement. All patients included in the study had an unambiguous clinic note from the attending surgeon, the medical oncologist, or both stating that the disease was stage 3 according to the aforementioned definitions, which was further verified by evaluation of the cross-sectional imaging reports. In addition, all patients were reviewed at a multidisciplinary conference, at which imaging was reviewed and treatment strategy recommended.

FIG. 1 Flow chart with time frames expressed as median (range) (**a**). ▶ Sixty-four year old female with a 5.7 cm tumor at the tail of the pancreas encasing the celiac axis, superior mesenteric artery (SMA), and the left renal vein. After induction therapy with FOLFIRINOX the maximal tumor diameter decreased by 30 % (to 4 cm) and the patient underwent distal pancreatectomy (**b**). Sixty-two year old male with a 2.2 cm pancreatic neck tumor and an unreconstructable encasement of the superior mesenteric vein (SMV) below the portal splenic confluence. After 3 months of induction therapy with FOLFIRINOX only mild narrowing of the SMV was noted and the patient underwent Whipple's procedure (**c**)

The treatment schema is presented in Fig. 1a. The starting dose intensity of FOLFIRINOX induction therapy was 80 % of that used in the PRODIGE/ACCORD trial.[1] Dose reductions or delays were instituted at the discretion of the treating medical oncologist. Typically, restaging of computerized tomography (CT) and CA 19-9 measurements were performed to assess tumor response and resectability after four cycles. At this point, conversion to resectable disease was reassessed at the multidisciplinary meeting. Decisions were made on a case-by-case basis. Distant progression was defined as new distant metastases, determined either by imaging or at surgical exploration. Patients who appeared to convert to resectable disease underwent surgical exploration, and patients with stable disease were typically initiated with chemoradiotherapy (CRT). Similarly, all patients who appeared to convert to resectable disease after CRT went on to surgical exploration. When distant progression occurred under induction therapy or when disease remained unresectable after completion of the protocol, patients typically continued with systemic therapy or were managed with best supportive care.

Radiographic response was evaluated in a prospective manner by two radiologists. Response was reported according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines.[16] The ORR was defined as the percentage of patients who had more than a 30 % decrease in the greatest dimension of the primary tumor or complete disappearance of the primary tumor. Pathologic response also was recorded, and the guidelines used to determine this response have been reported previously.[5]


A
STAGE III PDAC
Induction **FOLFIRINOX** (n=101)
3 mo (0.5-11mo)
5 mo (3-15mo)
Restaging CT
Resectable (n=16)
Unresectable (n=85)
OR
Distant Progression (n=22)
Stable Disease (n=63)
Resected (n=15)
Unresectable Peritoneal disease (n=1)
Chemoradiation
9 mo (4-13mo)
RESTAGING CT
Unresectable (n=44)
Distant progression (n=5)
Stable Disease (n=39)
Resectable
(n=19)
OR
Resected
(n=16)
Unresectable
Locally (n=3)


B
Before
After
PV
Tumor
SMA
Kidney
PV
Tumor
SMA
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Origin of
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Aorta
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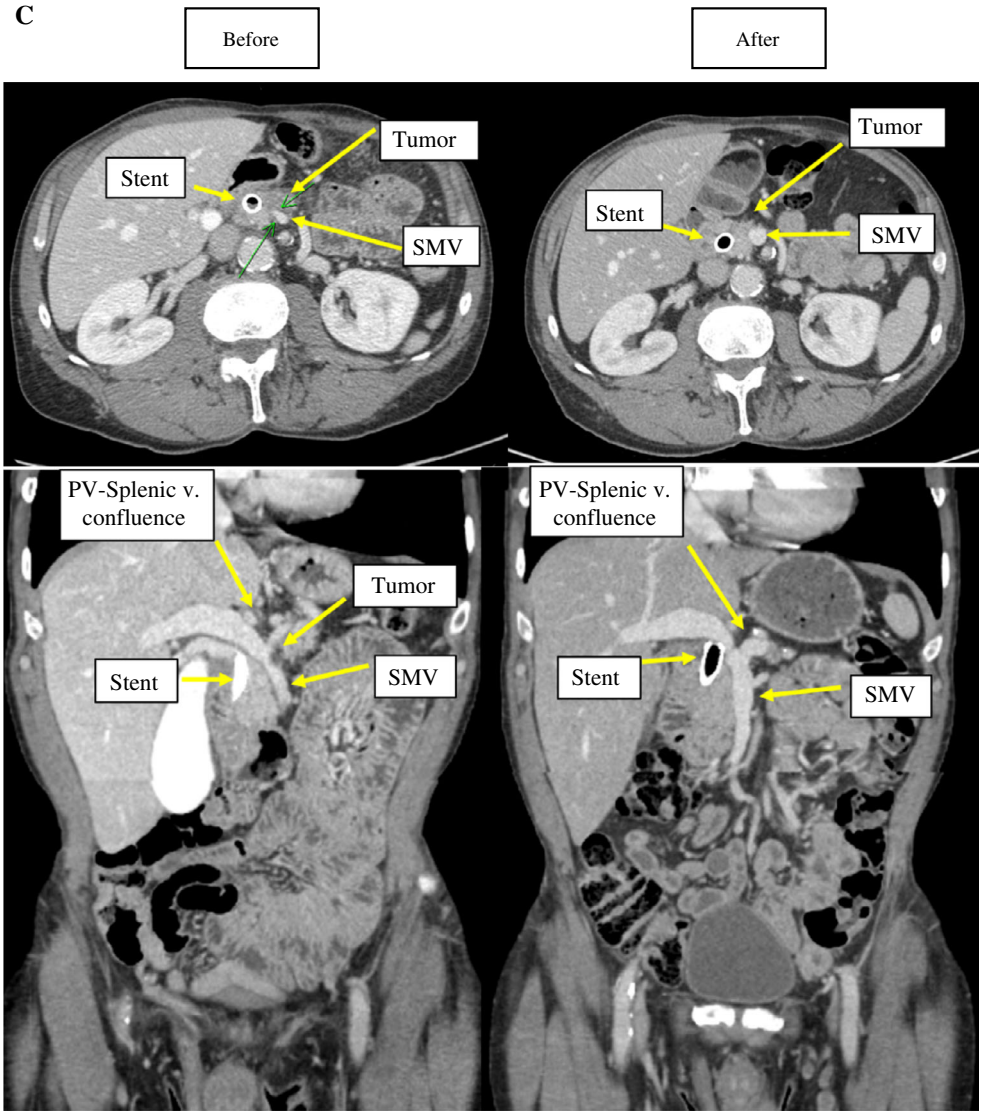
FIG. 1 continued



Toxicity was graded according to the National Cancer Institute criteria.[17] Only toxicities greater than grade 1 were recorded. Operative morbidity is recorded and graded in the MSKCC Surgical Events database,[18] which uses a severity scale similar to others published previously.[19]

Data Analysis

Descriptive and comparative statistics were calculated using Statistical Software for the Social Sciences (SPSS) version 22 software (SPSS, Chicago, IL, USA). Continuous variables were compared using Student's *t* test or the Mann–Whitney test as appropriate by the type of distribution. Categorical variables were compared using Chi square or Fisher's exact test depending on the number of observations. A *p* value of 0.05 or lower was considered significant. Survival distributions were estimated using the Kaplan–Meier method. Time to event was calculated from the initiation date of induction therapy with FOLFIRINOX to the date of the event. An event for progression-free survival (PFS) was defined as distant progression, recurrence (for resected patients), or death. Patients without the event of interest at the last follow-up visit were censored.

RESULTS

During the 3-year study period (July 2010 to October 2013), 101 patients were identified who were treated at our institution for stage 3 PDAC with induction FOLFIRINOX. Demographics and pretreatment tumor characteristics are summarized in Table 1A. The median age of all the patients was 64 years (range 37–81 years). Of these patients, 52 % were male, and 95 % were classified as Eastern Cooperative Oncology Group (ECOG) 0 or 1. The

TABLE 1 (A) Demographics and pretreatment tumor characteristics and (B) treatment characteristics

Characteristic	All patients ($n = 101$) n (%)	Resected ($n = 31$) n (%)	Unresectable ($n = 70$) n (%)	p value
(A)				
Age at diagnosis: years (range)	64 (37–81)	64 (43–81)	64 (37–80)	0.8
Male sex	53 (52)	18 (58)	35 (50)	0.5
Pretreatment biliary stent	44 (44)	17 (55)	27 (39)	0.1
Pre-treatment surgical exploration	11 (11)	4 (13)	7 (10)	0.7
ECOG				0.3
0	12 (12)	4 (13)	8 (11)	
1	84 (83)	24 (77)	60 (86)	
2	5 (5)	3 (10)	2 (3)	
Proximal tumor location[a]	72 (71)	23 (74)	49 (70)	0.8
Basis for unresectability				**0.001**
Celiac axis[b]	9 (9)	2 (6)	7 (10)	
SMA[c]	37 (37)	10 (33)	27 (39)	
Hepatic artery[d]	7 (7)	4 (13)	3 (4)	
Multiple (arterial & venous, >1 artery)	42 (42)	9 (29)	33 (47)	
Venous (PV, SMV)[e]	6 (6)	6 (19)	0	
Pretreatment size: cm (range)	3.5 (1.6–8.9)	3.2 (1.6–5.7)	3.65 (2–8.9)	**0.02**
Regional lymph nodes (*N*)				0.1
cN0	51 (50)	12 (39)	39 (56)	
cN1	50 (50)	19 (61)	31 (44)	
Pretreatment CA19-9: U/ml (range)	164 (1–16,960)	169 (1.9–16,960)	161 (1–8400)	0.3
Follow-up: months (range)[f]	12 (3–37)	15 (6–32)	11 (3–37)	0.2

Characteristic	All patients ($n = 101$) n (%)	Resected ($n = 31$) n (%)	Unresectable ($n = 70$) n (%)	p value
(B)				
Induction FOLFIRINOX ($n = 101$)				
FOLFIRINOX duration: weeks (range)	13 (2–43)	14 (2–38)	11 (2–43)	0.9
FOLFIRINOX cycles: *n* (range)	6 (1–20)	7 (1–18)	6 (1–20)	0.9
Grade 2 toxicity[g]	37 (37)	9 (29)	28 (40)	0.3
Grade 3 toxicity[g]	14 (14)	3 (10)	11 (16)	0.5
Dose reduction/delayed dose	45 (45)	11 (35)	34 (49)	0.2
Size after FOLFIRINOX: cm (range)	3 (1.4–8)	2.6 (1.4–5.5)	3.2 (1.7–8)	**0.005**
Size reduction after FOLFIRINOX (%)	−12 (–48 to 67)	−19 (–48 to 67)	−8.4 (–44 to 44)	0.08
Size reduction after FOLFIRINOX >10 %	51 (50)	22 (71)	29 (41)	**0.006**
Primary tumor (after FOLFIRINOX)				**<0.001**
ycT2	2 (2)	2 (6)	0	
ycT3	20 (20)	14 (45)	6 (9)	
ycT4	79 (79)	15 (48)	64 (91)	
CA19-9 reduction after FOLFIRINOX > 50 %	45 (50)	18 (78)	27 (40)	**0.001**

TABLE 1 continued

Characteristic	All patients ($n = 63$) n (%)	Resected ($n = 16$) n (%)	Unresectable ($n = 47$) n (%)	p value
Chemoradiation ($n = 63$)				
CRT regimen				0.7
No chemo-sensitizer	2 (3)	0	2 (5)	
5-FU	14 (22)	4 (25)	10 (21)	
Gemcitabine	47 (75)	12 (75)	35 (74)	

Continuous variables are expressed as median (range); categorical variables are expressed as n (%); p value refers to the comparison of the resected and unresectable groups

Bold values are statistically significant ($p < 0.05$)

ECOG Eastern Cooperative Oncology Group, *SMA* superior mesenteric artery, *PV* portal vein, *SMV* superior mesenteric vein, *CRT* chemoradiotherapy, *5-FU* 5-fluorouracil

[a] Head or uncinate location

[b] Celiac abutment

[c] Greater than 180° SMA encasement

[d] Long-segment encasement of the hepatic artery

[e] Unreconstructable SMV/PV

[f] From FOLFIRINOX initiation to last follow-up visit

[g] Toxicity of FOLFIRINOX induction therapy (without radiation)

median pretreatment diameter of the primary tumor was 3.5 cm (range 1.6–8.9 cm), which decreased significantly to a median diameter of 3 cm (range 1.4–8 cm; $p < 0.001$) at the completion of FOLFIRINOX therapy.

The pattern of vascular involvement that precluded resection differed between those who proceeded to resection and those who did not ($p < 0.001$). Celiac axis, superior mesenteric artery, and multiple vessel involvement were more common in the group that did not proceed to resection, whereas hepatic artery and unreconstructable venous involvement were more common in the group that experienced a response and proceeded to resection. No difference between the groups was noted for pretreatment regional lymph node status, CA 19-9, or carcinoembryonic antigen (CEA) levels.

Induction therapy with FOLFIRINOX comprised a median of six cycles (range 1–20 cycles) lasting 13 weeks (range 2–43 weeks). Toxicity above grade 1 was recorded for 50 %, and the highest toxicity grade was 3. No difference was noted between the groups who experienced response and proceeded to resection and those who did not regarding the grade of toxicity (Table 1B).

Dose reductions or delays were required for 45 % of the patients. Resectability was associated with a tumor size reduction greater than 10 % ($p = 0.006$) and a reduction in CA 19-9 greater than 50 % ($p = 0.001$) after FOLFIRINOX induction therapy (Table 1B; Fig. 2). Representative images from patients with response to FOLFIRINOX alone are presented in Fig. 1b, c.

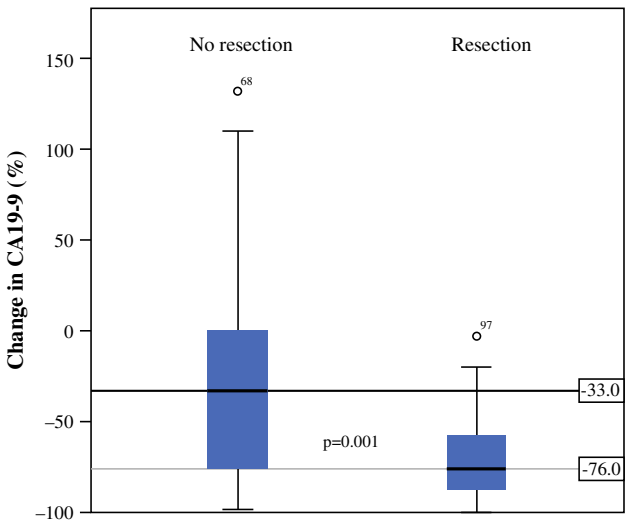


FIG. 2 Reduction in CA 19-9 after induction therapy with FOLFIRINOX stratified by resection groups. The horizontal *thick line* in the middle of *each box* indicates the median, whereas the upper and lower borders of the box mark the 75th and 25th percentiles, respectively. The *whiskers* above/below the *box*, extend to the most extreme point no longer than 1.5 times the interquartile range from the *box*. The points beyond the *whiskers* are outliers

At completion of the initial FOLFIRINOX induction course, 16 patients underwent surgical exploration, and 15 patients (15 %) underwent tumor resection (Fig. 1a). Distant progression developed in 23 patients (23 %), and the remaining 63 patients underwent chemoradiation. In this

TABLE 2 Outcome after completed protocol

Characteristic	All patients ($n = 101$) n (%)	Resected ($n = 31$) n (%)	Unresectable ($n = 70$) n (%)	p value
Size: cm (range)[a]	2.9 (1.1–8)	2.5 (1.1–4.7)	3.3 (1.6–8)	**<0.001**
Size reduction: % (range)[a]	−16 (−67 to 44)	−29 (−63 to 14)	−10 (−67 to 44)	**0.001**
Size reduction >30 %[a]	29 (29)	15 (48)	14 (20)	**0.004**
Primay tumor (T)[a]				**<0.001**
ycT2	2 (2)	2 (6)	0	
ycT3	33 (33)	25 (81)	8 (11)	
ycT4	66 (65)	4 (13)[b]	62 (89)	
ycN0[a]	86 (85)	23 (74)	63 (90)	**0.04**
CA19-9: U/ml (range)[c]	52 (0–2921)	41 (0–670)	63 (1–2921)	0.3
CA19-9 reduction >50 %[c]	45 (50)	18 (78)	27 (40)	**0.001**
CEA: ng/ml (range)[c]	4.1 (0.8–84.9)	3.6 (0.8–29.6)	4.1 (0.9–84.9)	0.5
Surgical exploration[a]	35 (35)	31 (100)	4 (6)	–
Resection rate[a]	31 (31)	–	–	–
R0 resection rate	–	16 (55)[d]	–	–

Induction FOLFIRINOX therapy with or without subsequent chemoradiation therapy. Continuous variables are expressed as median (range); categorical variables are expressed as n (%); p value refers to the comparison of the resected and unresectable groups

Bold values are statistically significant ($p < 0.05$)

[a] After protocol

[b] Four patients were classified as ycT4 and underwent Appleby operation ($n = 3$) and hepatic artery resection ($n = 1$)

[c] After FOLFIRINOX

[d] Calculated for 29 patients (pathology report is pending for 2 patients)

group 63 patients, 5 patients experienced overt metastases after chemoradiation, 16 patients underwent tumor resection, and 42 patients had stable unresectable disease.

Table 2 summarizes the results for all the patients at completion of FOLFIRINOX induction therapy with or without chemoradiation. Resectability was associated with posttreatment tumor size, nodal status, or decrease in CA 19-9 level. The ORR was 29 % (20 % without chemoradiation), and approximately 50 % of the patients who achieved a partial response (>30 % size reduction) underwent tumor resection. Overall, 31 % of the patients (31 patients) underwent tumor resection, with 55 % (16 patients) achieving an R0 resection.

The median duration of systemic treatment, chemoradiation, or both in the group of patients who underwent resection was 7 months (range 3–15 months). Table 3 shows the characteristics of the patients who underwent tumor resection. The selective use of radiation therapy was associated with a lower R0 rate (33 vs 79 %; $p = 0.02$), a higher vascular resection rate (47 vs 7 %; $p = 0.03$), a higher pN0 rate (80 vs 28 %; $p = 0.009$), and a higher rate of greater than 50 % pathologic response (75 vs 22 %; $p = 0.03$). No perioperative mortality occurred.

The median follow-up period for our cohort was 12 months (range 3–37 months). The median overall survival (OS) period was 25 months (confidence interval [CI] 19–31 months), and the median PFS period was 16 months (CI 14–18 months). The patients who progressed during induction FOLFIRINOX therapy experienced a median OS of 11 months (CI 9–13 months), and the patients who did not progress had a median OS of 26 months (CI 20–32 months) (Fig. S1). At this writing, the median OS has not been reached in the group of patients who underwent tumor resection. In the group of patients who had stable disease after systemic therapy and chemoradiation, the median survival period was 26 months (CI 18–33 months).

DISCUSSION

The current study of FOLFIRINOX induction therapy in stage 3 PDAC patients showed an ORR of 20 %, which increased to 29 % with the selective use of radiation therapy. In addition, a high proportion (31 %) of initially stage 3 (locally unresectable) patients was converted to resectable disease. The ability to perform resection was

TABLE 3 Patients who underwent tumor resection stratified by radiation therapy

Characteristic	All patients ($n = 31$) n (%)	Radiation ($n = 16$) n (%)	No radiation ($n = 15$) n (%)	p value
Interval between FOLFIRINOX initiation and resection: months (range)	7 (3–15)	9 (4–13)	5 (3–15)	0.09
Vascular resection	8 (28)	7 (47)	1 (7)	**0.03**
Major postoperative complication (Grades 3 & 4)	6 (20)	5 (31)	1 (7)	0.2
Hospital stay: days (range)	6 (3–27)	6.5 (3–27)	6 (4–9)	0.4
60-day readmission	7 (23)	5 (31)	2 (14)	0.4
R0 resection rate[a]	16 (55)	5 (33)	11 (79)	**0.02**
Primary tumor (T)[a]				0.5
ypT2	1 (3)	0	1 (7)	
ypT3	28 (97)	15 (100)	13 (93)	
Regional lymph nodes (N)[a]				**0.009**
ypN0	16 (55)	12 (80)	4 (29)	
ypN1	13 (45)	3 (20)	10 (71)	
Pathologic response (%)[b]				**0.03**
0–24	4 (19)	2 (17)	2 (22)	
25–49	6 (29)	1 (8)	5 (56)	
50–99	11 (52)	9 (75)	2 (22)	
100	0	0	0	
Pathologic response >50 %[b]	11 (52)	9 (75)	2 (22)	**0.03**
Poorly differentiated tumor	9 (31)	4 (27)	5 (36)	0.7
Lymphovascular invasion	14 (48)	7 (47)	7 (50)	0.8
Perineural invasion	21 (72)	11 (73)	10 (71)	1

Continuous variables are expressed as median (range); categorical variables are expressed as n (%); p value refers to the comparison of the radiation and no radiation groups

Bold values are statistically significant ($p < 0.05$)

[a] Pathology reports were available for 29 patients

[b] Pathologic response was recorded in 21 cases

associated with either radiographic response or a reduction in serum CA 19-9. The safety profile of this regimen in this group of patients was encouraging, with no grade 4 or 5 toxicities. Only 14 % of the patients experienced grade 3 toxicity.

The current study was designed to evaluate only those patients deemed locally unresectable (stage 3) at the time of diagnosis. Patients with borderline resectable tumors (stage 1 or 2) were excluded.

Defining the differences between borderline resectable and locally unresectable tumors is challenging, especially in a retrospective study. To minimize selection bias and possible inclusion of borderline resectable patients, the institutional cancer database was queried for all stage 3 patients treated with FOLFIRINOX. In addition, tumor stage was verified by medical chart and imaging report review. Only patients with an unambiguous clinic note that defined locally unresectable disease were included in the study, and all the included patients were reviewed at a multidisciplinary conference.

The ORR often is used as a surrogate for outcome. Conroy et al.[1] presented results from a randomized phase 3 trial of stage 4 PDAC patients, showing a superior ORR (32 vs 9 %) for FOLFIRINOX compared with single-agent gemcitabine, which also was associated with improved outcome.

A recent phase 2 study from our institution reported an ORR of 10 % for stages 1 and 2 patients treated with preoperative gemcitabine and oxaliplatin therapy.[4] Similarly, an ORR of 12 % was reported by the group from MD Anderson Cancer Center for borderline resectable patients treated with gemcitabine-based regimens.[20] Only two studies, which included a mix of borderline (stages 1 and 2) and locally unresectable (stage 3) PDAC patients treated initially with FOLFIRINOX, have reported the ORR of FOLFIRINOX in the non-metastatic setting. A recent report from the Massachusetts General Hospital (MGH) group[3] described 22 patients with an ORR of 27 %, and a French multicenter study reported on 77 patients with an ORR of 28 %.[2] Our findings of a 20 % ORR (without

radiation) and a 29 % ORR with selective radiation therapy are similar, suggesting that response to FOLFIRINOX may be superior to that of other reported regimens.

The aforementioned ORRs display a consistent pattern, in which the ORR with FOLFIRINOX is at least twofold higher than that with non-FOLFIRINOX regimens.[1,4] It should be noted, however, that a high ORR (23 %) was recently reported for stage 4 PDAC patients in a phase 3 randomized trial that evaluated a novel regimen of nab-paclitaxel plus gemcitabine.[21] However, FOLFIRINOX and gemcitabine/nab-paclitaxel have not been compared in a randomized fashion in any disease setting.

The primary aim of the current study included evaluation of the rate for conversion from unresectable to resectable disease. This therapeutic goal is of importance because a previous study by our group suggested that patients able to undergo resection after initial systemic treatment of stage 3 disease have a survival similar to those whose tumors are initially resected.[5]

In the current study, 31 % of the patients initially deemed unresectable eventually underwent resection. Similar rates of conversion also have been reported from other institutions. The group from Pittsburgh[22] reported on 13 stage 3 PDAC patients treated with FOLFIRINOX induction therapy, from which 2 patients (15 %) underwent resection, and the R0 rate was 50 % (1 patient). Hosein et al.[23] evaluated 14 stage 3 PDAC patients treated with FOLFIRINOX induction therapy, from which 43 % (6 patients) were resected and 83 % (5 patients) achieved R0 resection. Ferrone et al.[14] recently reported on 40 patients (both borderline [stage 1 or 2] and locally unresectable [stage 3] PDAC patients) treated with preoperative FOLFIRINOX and concluded that after preoperative FOLFIRINOX, imaging no longer predicts resectability. These results are interesting, however, because their study looked only at patients taken to the operating room, it is unclear what imaging factors were used for this selection in their report. The current study, which included all patients treated with FOLFIRINOX for stage 3 PDAC found that resectability was associated with either radiographic response or CA 19-9 reduction.

It does appear that resectability rates are higher after FOLFIRINOX than after non-FOLFIRINOX regimens,[6–13] for which the resectability rates for locally unresectable (stage 3) patients treated with induction therapy have ranged between 7 and 19 %. Small et al.[9] reported a multi-institutional phase 2 study that assessed the efficacy of gemcitabine with concurrent radiation therapy in non-metastatic PDAC patients. The authors found that only 1 (7 %) of 14 patients with an initial diagnosis of locally unresectable tumor (stage 3) underwent resection after therapy. Although methodologic limitations preclude a definitive conclusion, the current results, which identified a resection rate of 31 % and a R0 resection rate of 55 % in a homogeneous group of 101 stage 3 PDAC patients, suggest that the response evident after induction FOLFIRINOX therapy may be better than that after previous, primarily gemcitabine-based regimens.

As an observational study, this analysis had inherent selection limitations, and the generalizability of these outcome and toxicity results may well be restricted to selected patients treated at specialized high-volume centers. Therefore, causality cannot be determined in a nonrandomized trial, and the selective use of radiation therapy further compounds the direct effect of FOLFIRINOX treatment. A major advantage of this study was the intention-to-treat analysis with a denominator that included all stage 3 PDAC patients (locally unresectable) treated with induction FOLFIRINOX therapy whether their tumor was resected or not. This was a homogeneous population treated with the same regimen.

CONCLUSION

This study demonstrated that nearly one third of patients initially identified to have stage 3 pancreatic carcinoma and treated with FOLFIRINOX responded radiographically and underwent tumor resection. Radiographic response and reduction in serum CA 19-9 were associated with this outcome. Prospective trials are needed to validate these results and to determine whether they will be translated into survival benefit.

ACKNOWLEDGMENT This study was funded in part by NIH/NCI Cancer Center Support Grant P30 CA008748.

DISCLOSURE There are no conflicts of interest.

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