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FOLFIRINOX induction therapy for stage III pancreatic adenocarcinoma

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Abstract

Background—FOLFIRINOX therapy for pancreatic ductal adenocarcinoma (PDAC) has been reported to result in objective response rates that are 2–3 fold higher than other regimens. Our goal was to assess response rates and resection rates in locally unresectable (stage III) patients initially treated with induction FOLFIRINOX.

Methods—The institutional cancer database was queried for patients treated with induction FOLFIRINOX therapy between 2010–2013. Patients were included if they were treated at our institution for stage III PDAC (locally unresectable) that had been adjudicated at a weekly multidisciplinary tumor board.

Results—One hundred and one patients were identified. The median age was 64 years (range: 37–81) and the median follow-up was 12 months (range:3–37). Patients received a median of six cycles of induction FOLFIRINOX(range:1–20). No grade 4–5 toxicity was recorded. At initial restaging(median of 3 months following diagnosis), 23 patients(23%) had developed distant metastases, 15 patients(15%) underwent resection, and 63 patients(63%) proceeded to chemoradiation. Within the group of 63patients who proceeded to chemoradiation(median of 9 months following diagnosis), an additional 16 patients(16%) underwent resection and 5(5%) developed metastases. A partial radiographic response was observed in 29% of all patients, which was associated with the ability to perform resection(p=0.004). The median overall survival within the group who progressed on FOLFIRINOX and the group who did not progress were 11 and 26months, respectively.

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Conflict of interest: All authors declare that they have no conflict of interests regarding this study.

Conclusion—Nearly a third of patients who had been initially identified to have stage III pancreatic carcinoma and had been treated with FOLFIRINOX responded radiographically and underwent tumor resection.

Keywords

pancreas; FOLFIRINOX; adenocarcinoma; induction; chemotherapy; radiation

INTRODUCTION

A recently completed phase III randomized trial for stage IV PDAC identified FOLFIRINOX to be superior to gemcitabine with respect to radiographic response along with improved progression-free and overall survival[1]. Patients who received FOLFIRINOX experienced a 32% objective response rate (ORR) compared to 9% in the gemcitabine arm, which correlated with survival benefit (median overall survival and progression-free survival: 11 and 6 months vs 7 and 3 months, respectively). Retrospective studies of patients with both borderline resectable PDAC (stage I–II) and stage III patients(locally unresectable) have also 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 II 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 with induction therapy is an important therapeutic goal for stage III patients, which studies suggest is associated with improved survival[5]. During the pre-FOLFIRINOX era, the conversion rates of stage III patients with induction therapy ranged between 7–19%[6–13]. Currently, the resectability rates after induction FOLFIRINOX for stage III PDAC are not established, as recent series assessing FOLFIRINOX for non-metastatic patients have been either single-arm surgical series with a denominator limited to selected patients who were 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 III PDAC patients treated with induction FOLFIRINOX therapy at our institution, whether or not their tumor was resected. This study presents a comprehensive evaluation of FOLFIRINOX induction therapy for all patients who presented with stage III 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 III PDAC and then were treated with induction FOLFIRINOX therapy was performed. This search identified 106

patients who were treated at Memorial Sloan Kettering Cancer Center (MSKCC) between 2010–2013. Five patients were excluded by chart review, as three patients were considered borderline resectable (encasement of the portal vein accompanied by marked lymphadenopathy) and another 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 III disease was defined according to the National Comprehensive Cancer Network definitions[15]. Only patients categorized as T4, any N, M0 were included. No patients had extra-regional metastatic disease. Further description of findings consistent with local unresectability included the following: greater than 180 degrees SMA encasement, any celiac abutment, inferior vena cava, unreconstructable SMV/portal occlusion, and aortic invasion or encasement. All patients who were included had an unambiguous clinic note from the attending surgeon and/or the medical oncologist that stated the disease was stage III according to the above mentioned definitions, which were further verified by evaluation of the cross-sectional imaging reports. In addition, all patients were reviewed at a multidisciplinary conference, where imaging was reviewed and treatment strategy recommended. The treatment schema is presented in Figure 1A. FOLFIRINOX induction therapy was administered with a starting dose intensity 80% from that used in the PRODIGE/ACCORD trial[1]. Dose reductions or delays were instituted at the discretion of the treating medical oncologist. Typically, restaging CT and CA 19-9 measurements were performed to assess tumor response and resectability after 4 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, which was 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 guidelines (RECIST, version 1.1)[16]. Objective response rate(ORR) was defined as the percentage of patients who had a decrease >30% in the greatest dimension of the primary tumor or complete disappearance of the primary tumor. Pathologic response was also recorded, and the guidelines utilized for determining this response have been previously reported[5].

Toxicity was graded according to the National Cancer Institute criteria[17]. Only toxicities above 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 previously published[19].

Data analysis

Descriptive and comparative statistics were performed using Statistical Software for the Social Sciences(SPSS) version 22 software. Continuous variables were compared using the Student t test or Mann-Whitney test, as appropriate by the type of distribution. Categorical variables were compared using $\chi 2$ or the Fisher exact test depending on the number of observations. A p-value ≤ 0.05 was considered significant. Survival distributions were estimated using the Kaplan-Meier method. Time to event was calculated from initiation date of induction therapy with FOLFIRINOX to date of 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 last follow-up were censored.

RESULTS

During the three-year study period (July 2010 to October 2013), 101 patients were identified who were treated at our institution for stage III PDAC with induction FOLFIRINOX. Demographics and pretreatment tumor characteristics are summarized in Table 1A. The median age of all patients was 64 years (range:37–81 years), 52% were male, and 95% were ECOG 0-1. The median pretreatment diameter of the primary tumor was 3.5cm (range:1.6–8.9), which significantly decreased to a median diameter of 3cm (range:1.4–8; $p<0.001$) 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(SMA), 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 response and proceeded to resection. No difference between the groups was noted for pretreatment regional lymph nodes status, CA 19-9, or CEA levels.

Induction therapy with FOLFIRINOX consisted of a median of six cycles(range:1–20) lasting 13 weeks(range:2–43). 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 with respect to the grade of toxicity(Table 1B). Dose reductions or delays were required in 45% of the patients. Resectability was associated with tumor size reduction >10%($p=0.006$), and with greater than 50% reduction in CA 19-9 ($p=0.001$) after FOLFIRINOX induction therapy(Table 1B and Figure 2). Representative images from patients with response to FOLFIRINOX alone, are presented in Figure 1B–C. Upon completion of the initial FOLFIRINOX induction course, 16 patients underwent surgical exploration and 15(15%) underwent tumor resection(Figure 1A). Distant progression developed in 23 patients (23%) and the remaining 63 patients underwent chemoradiation. Within this group of 63 patients, five developed overt metastases following chemoradiation, 16 underwent tumor resection, and 42 had stable unresectable disease.

Table 2 summarizes the results of all patients upon completion of FOLFIRINOX induction therapy with or without chemoradiation. Resectability was associated with post-treatment tumor size, nodal status, or decrease in CA 19-9 level. The ORR was 29%(20% without chemoradiation) and approximately 50% of patients who achieved partial response(more than 30% size reduction) underwent tumor resection. Overall, 31%(31 patients) underwent

tumor resection from which 55%(16 patients) achieved an R0 resection. Median duration of systemic treatment and/or chemoradiation within the group of patients who underwent resection was seven months (range:3–15months). Table 3 shows the characteristics of patients who underwent tumor resection. The selective use of radiation therapy was associated with lower R0 rates (33% vs. 79%, p=0.02), higher vascular resection rates (47% vs. 7%, p=0.03), higher pN0 rate (80% vs. 28%, p=0.009), and higher rate of pathological response greater than 50%(75% vs. 22%, p=0.03). No perioperative mortality occurred.

The median follow-up of our cohort was 12 months (range:3–37). Median overall survival (OS) and progression-free survival (PFS) were 25 months (CI:19–31) and 16 months (CI: 14–18), respectively. Patients who progressed during induction FOLFIRINOX therapy experienced a median OS of 11 months (CI:9–13) and patients who did not progress had a median OS of 26 months (CI:20–32)(Figure S1). The median OS has not been reached in the group of patients who underwent tumor resection. Within the group of patients who had stable disease following systemic therapy and chemoradiation the median survival was 26 months (CI:18–33).

DISCUSSION

The current study of FOLFIRINOX induction therapy in stage III PDAC patients was associated with an objective response rate of 20%, which increased to 29% with the selective use of radiation therapy. In addition, a high proportion (31%) of initially stage III (locally unresectable) patients were converted to resectable disease. The ability to perform resection was associated with either radiographic response or a reduction in serum CA19-9. The safety profile of this regimen within this group of patients was encouraging with no grade 4–5 toxicities. Only 14% of patients experienced grade 3 toxicity.

The present study was designed to evaluate only those patients who were deemed locally unresectable (stage III) at the time of diagnosis. Patients with borderline resectable tumors (stage I–II) were excluded. Defining the differences between borderline resectable and locally unresectable tumors is challenging, especially in a retrospective study. In order to minimize selection bias and possible inclusion of borderline resectable patients, the institutional cancer database was queried for all stage III 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, and all of the included patients were reviewed at a multidisciplinary conference.

Objective response rate (ORR) is often used as a surrogate for outcome. Conroy et al[1] presented results from a randomized phase III trial of stage IV PDAC patients and reported a superior ORR (32% vs 9%) for FOLFIRINOX compared with single-agent gemcitabine, which was also associated with improved outcome. A recent phase II study from our institution reported an ORR of 10% in stage I–II 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 (stage

I–II) and locally unresectable (stage III) PDAC patients treated initially with FOLFIRINOX, have reported the ORR of FOLFIRINOX in the non-metastatic setting. A recent report from the 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, and suggest that response to FOLFIRINOX may be superior to other reported regimens. The above ORRs display a consistent pattern, in which the ORR with FOLFIRINOX is at least two-fold higher compared to non-FOLFIRINOX regimens[1,4]. It should be noted however, that a high ORR(23%) was recently reported in stage IV PDAC patients in a phase III randomized trial that evaluated a novel regimen of nab-paclitaxel plus gemcitabine[21]. 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 conversion rate from unresectable to resectable disease. This therapeutic goal is of importance, as a previous study by our group has suggested that patients who are able to undergo resection following initial systemic treatment of stage III disease experience similar survival to those whose tumors are initially resected[5]. Within the current study, 31% of patients initially deemed unresectable eventually underwent resection. Similar rates of conversion have also been reported from other institutions. The group from Pittsburgh[22] reported on 13 stage III PDAC patients treated with FOLFIRINOX induction therapy, from which 2(15%) underwent resection and the R0 rate was 50%(1 patient). Hosein et al[23] evaluated 14 stage III 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 I–II) and locally unresectable (stage III) PDAC patients) treated with preoperative FOLFIRINOX and concluded that after preoperative FOLFIRINOX, imaging no longer predicts resectability. These results are interesting, however since their study only looked at patients who were 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 III PDAC patients found that resectability was associated with either radiographic response or CA 19-9 reduction.

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

As an observational study, this analysis has 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 non-randomized trial and the selective use of radiation therapy further compounds the direct effect of FOLFIRINOX treatment. A major advantage of this study is the intention-to-treat analysis with a denominator that includes all stage III PDAC patients (locally unresectable) treated with induction FOLFIRINOX therapy, whether or not their tumor was resected. This is a homogeneous population treated with the same regimen.

CONCLUSION

This study demonstrates that nearly a third of patients who had been initially identified to have stage III pancreatic carcinoma and had been treated with FOLFIRINOX responded radiographically and underwent tumor resection. Radiographic response and reduction in serum CA19-9 were associated with this outcome. Prospective trials are needed to validate these results and determine whether they will be translated into survival benefit.

Acknowledgments

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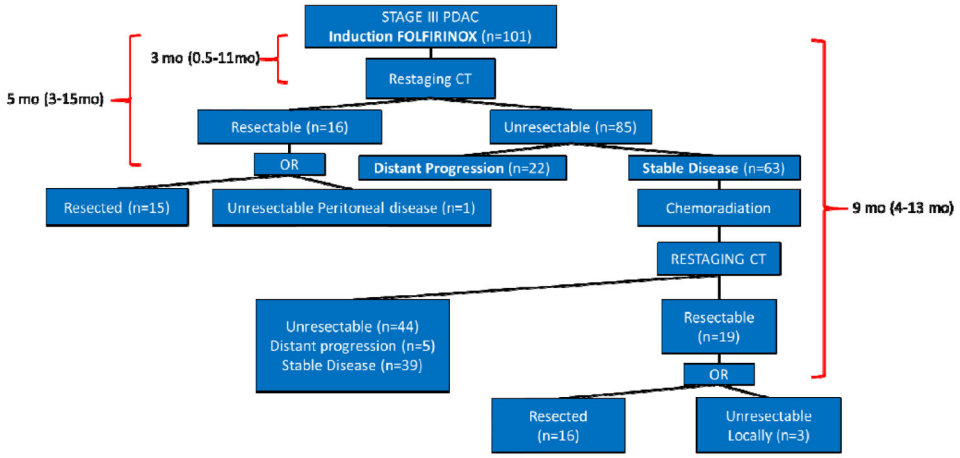
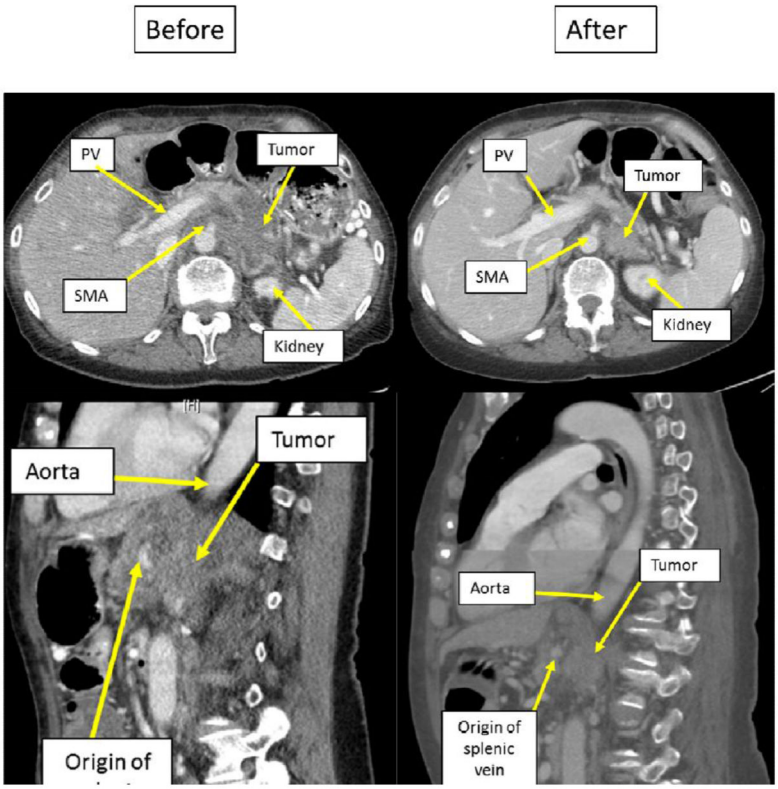
A.





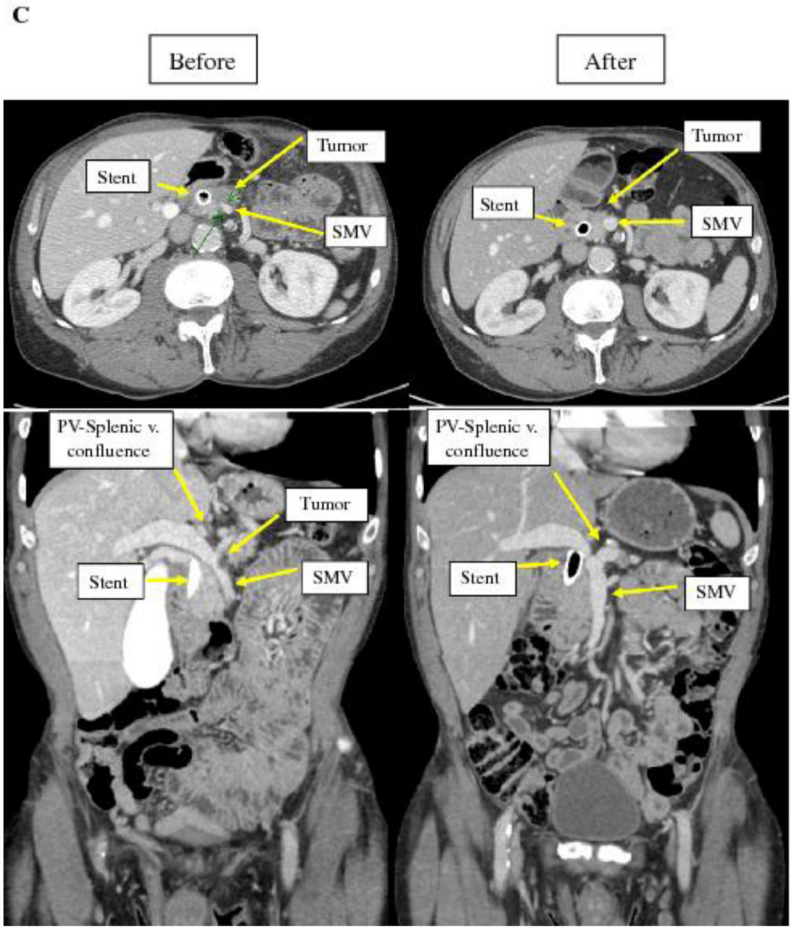


Figure 1.

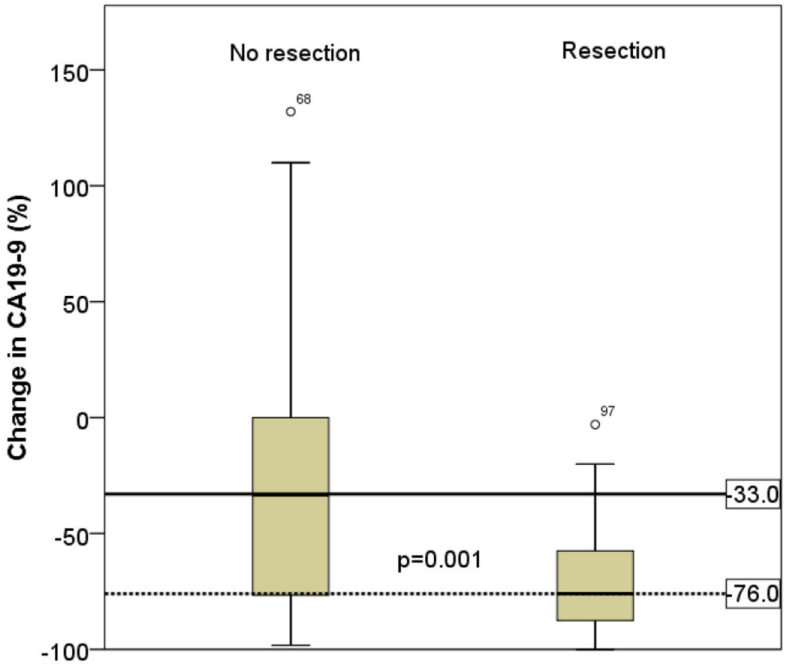


Figure 2.

Table 1

Table 1A. Demographics and pretreatment tumor characteristics

Characteristic	All patients (n=101)	Resected (n=31)	Unresectable (n=70)	*p*-value
Age at diagnosis	64 (37–81)	64 (43–81)	64 (37–80)	0.8
Male sex	53 (52%)	18 (58%)	35 (50%)	0.5
Pre-treatment 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[1] tumor location	72 (71%)	23 (74%)	49 (70%)	0.8
Basis for unresectability:				**0.001**
Celiac axis[2]	9 (9%)	2 (6%)	7 (10%)	
Superior mesenteric artery[3]	37 (37%)	10 (33%)	27 (39%)	
Hepatic Artery[4]	7 (7%)	4 (13%)	3 (4%)	
Multiple (arterial & venous, more than 1 artery)	42 (42%)	9 (29%)	33 (47%)	
Venous[5] (PV, SMV)	6 (6%)	6 (19%)	0	
Pretreatment size, cm	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, Units/ml	164 (1–16960)	169 (1.9–16960)	161 (1–8400)	0.3
Follow-up[6], months	12 (3–37)	15 (6–32)	11 (3–37)	0.2

Table 1B. Treatment characteristics

	Induction FOLFIRINOX (n=101)			
Characteristic	**All patients (n=101)**	**Resected (n=31)**	**Unresectable (n=70)**	***p*-value**
FOLFIRINOX Duration, weeks	13 (2–43)	14 (2–38)	11 (2–43)	0.9
FOLFIRINOX cycles	6 (1–20)	7 (1–18)	6 (1–20)	0.9
Grade 2 toxicity[7]	37 (37%)	9 (29%)	28 (40%)	0.3
Grade 3 toxicity[7]	14 (14%)	3 (10%)	11 (16%)	0.5
Dose reduction / delayed dose	45 (45%)	11 (35%)	34 (49%)	0.2

Table 1B. Treatment characteristics

Induction FOLFIRINOX (n=101)				
Characteristic	**All patients (n=101)**	**Resected (n=31)**	**Unresectable (n=70)**	***p*-value**
Size after FOLFIRINOX, cm	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**

Chemoradiation (n=63)				
Characteristic	**All patients (n=63)**	**Resected (n=16)**	**Unresectable (n=47)**	***p*-value**
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 vs. unresectable groups. CRT – chemoradiation therapy.

[1] Head or uncinate location.

[2] celiac abutment

[3] Greater than 180 degrees SMA encasement

[4] Long segment encasement of the hepatic artery.

[5] Unreconstructable superior mesenteric vein (SMV) / portal vein (PV)

[6] From FOLFIRINOX initiation to last follow-up

[7] Toxicity of FOLFIRINOX induction therapy (without radiation).

Table 2

Outcome after Completed Protocol[A].

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

Continuous variables are expressed as median (range); categorical variables are expressed as n (%).*P*-value refers to the comparison of the resected vs. unresectable groups.

[A] Induction FOLFIRINOX therapy with or without subsequent chemoradiation therapy.

[B] After protocol

[C] After FOLFIRINOX

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

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

Table 3

Patients who underwent tumor resection stratified by radiation therapy.

Characteristic	All patients (n=31)	Radiation (n=16)	No radiation (n=15)	*p*-value
Interval between FOLFIRINOX initiation and resection, months	7 (3–15)	9 (4–13)	5 (3–15)	0.09
Vascular resection	8 (28%)	7 (47%)	1 (7%)	**0.03**
Major post-operative complication (grade 3, 4)	6 (20%)	5 (31%)	1 (7%)	0.2
Length of stay, days	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[1]	16 (55%)	5 (33%)	11 (79%)	**0.02**
Primary Tumor (T)[1]				0.5
ypT2	1 (3%)	0	1 (7%)	
ypT3	28 (97%)	15 (100%)	13 (93%)	
Regional lymph nodes (N)[1]				**0.009**
ypN0	16 (55%)	12 (80%)	4 (29%)	
ypN1	13 (45%)	3 (20%)	10 (71%)	
Pathological response[2]				**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	
Pathological response[2]**>50%**	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 vs. no radiation groups.

[1] Pathology reports were available for 29 patients.

[2] Pathological response was recorded in 21 cases.