Published in final edited form as:

J Surg Oncol. 2018 March ; 117(3): 354–362. doi:10.1002/jso.24872.

Primary systemic therapy in resectable pancreatic ductal adenocarcinoma using mFOLFIRINOX: A pilot study

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Abstract

Background and Objectives—Surgery followed by gemcitabine and/or a fluoropyrimidine is standard therapy for resectable PDAC. mFOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m² Day 1, 5-FU 2400 mg/m² × 48 h IV, peg-filgrastim 6 mg SQ day 3, every 14 days) has substantial activity in metastatic PDAC. We wished to determine the tolerability/efficacy of peri-operative mFOLFIRINOX in resectable PDAC.

Methods—Patients with resectable PDAC (ECOG PS 0/1) received four cycles of mFOLFIRINOX pre- and post-surgery. The primary endpoint was completion of preoperative chemotherapy plus resection. Secondary endpoints included completion of all therapy, R0 resection, treatment related toxicity, PFS, and OS.

Results—Twenty-one patients enrolled: median age 62 (47–78); 20/21 (95%) completed four cycles of preoperative mFOLFIRINOX; response by RECIST was 1 CR, 3 PR, 16 SD; 17/21 (81%) completed resection, 16/21 (76%) R0; 14/21 (66%) completed four cycles of postoperative mFOLFIRINOX. Grade 3 and 4 toxicity occurred in 23% and 14% patients pre-operatively, 26% and 6.0% post-operatively. Nine patients are alive with median follow-up of 27.7 (3.1–47.1) months.

Conclusions—PST using mFOLFIRINOX in resectable PDAC is feasible and tolerable. R0 resection rate is high and survival promising, requiring longer follow-up and larger studies for definitive assessment.

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Keywords

cancer; chemotherapy; FOLFIRINOX; pancreatic; resectable

1 | INTRODUCTION

Pancreatic ductal adenocarcinoma is a highly lethal disease. It is estimated that in 2017 there will be 53 670 new cases and 43 090 deaths in the United States, which now ranks third among cancer related deaths.¹ At the time of diagnosis, roughly 38% of patients have disease which appears to be localized to the pancreas without obvious metastases.² Of those patients deemed operable on clinical grounds, 20–57% are found to have inoperable disease on exploration depending on the extent and nature of preoperative staging.^{3–5} Most patients present with unsuspected metastatic disease, borderline resectable tumors, or locally advanced, unresectable disease owing to involvement of critical vascular structures: superior mesenteric artery (SMA), celiac trunk, common hepatic artery, or superior mesenteric vein (SMV)/portal vein. Despite recent advances in systemic therapy, even those fortunate few who are able to undergo immediate surgery remain largely incurable, with a 5-year survival of 25–30% at best.^{6,7}

It is clear from these data that two parallel initiatives are essential if we are to improve patient survival. The first is any strategy that will result in an increase in successful R0 resection of the primary tumor and regional nodes (microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed).^{8,9} The second, of equal importance, is any strategy that will effectively prevent the establishment of occult micro-metastatic disease and the subsequent emergence of drug resistance. Given that clinically localized disease is often found to be unresectable at the time of surgery owing to the presence of occult metastatic disease,¹⁰ and that positive surgical margins are noted in 40–50% of cases,¹¹ early treatment of micro-metastatic disease and concomitantly of apparently resectable primary tumors could significantly increase the chances of effective surgery. Preoperative systemic treatment prior to any attempt at surgical intervention is one possible strategy with the potential to address both of these objectives. This strategy has proven useful in the treatment of other cancers such as esophageal, gastric, rectal, breast, and bladder.^{12,13} Additional benefits of primary systemic therapy include the ability to determine efficacy of the regimen, the detection of biologically aggressive tumors not suitable for surgery and the greater likelihood of completing all intended therapy. The administration of chemotherapy following surgery has been challenging, as fully 22–25% of patients do not complete the planned course of treatment.^{14,15}

This approach has now been explored in clinically resectable, borderline resectable, and locally advanced unresectable pancreatic cancer. The majority of studies have been single arm, single institution phase I/II studies which have often used minimally active regimens, no uniformity of classification and sporadic use of radiation therapy, and as a consequence results have been mixed.^{16–19} A comprehensive meta-analysis and systematic review of PST in both resectable and unresectable pancreatic cancer concluded that resection frequency and survival with PST in resectable patients was similar to that in patients undergoing primary

resection followed by adjuvant therapy.²⁰ A more recent propensity score matched analysis of PST followed by surgery versus upfront surgery in resectable disease, as well as a concurrent Cox regression analysis, from the National Cancer Database (NCDB) concluded that PST conferred a significant survival benefit in early stage disease.^{21,22} Given the very low response rates of the regimens used in the studies included in these retrospective analyses, one could potentially conclude that the previously mentioned ability to select patients for surgery based on the biology of their cancer, rather than any notable effect of the PST, was the principal reason for better outcomes to date with this strategy.

More active systemic therapy is needed to prospectively validate this approach and to improve on these results. FOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², 5FU 400 mg/m² IV on day 1, then 5FU 2400 mg/m² as a 46 h continuous infusion every 14 days) and gemcitabine plus nab-paclitaxel (gemcitabine 1000 mg/m², nab-paclitaxel 125 mg/m² D 1, 8, 15 IV every 28 days) are currently the most active regimens in a metastatic setting, with the former providing a median overall survival of 11.1 months and the latter 8.5 months in recent studies.^{23,24} FOLFIRINOX is now commonly modified with inclusion of peg-filgrastim, and elimination of the 5FU bolus (mFOLFIRINOX), with a resultant reduction in toxicity but not efficacy.²⁵

Thus, for the purposes of exploring the use of mFOLFIRINOX as PST in resectable pancreatic cancer, we have designed and completed a pilot study with the hypothesis that this regimen will be both feasible and tolerable and will be sufficiently active to provide a platform for future investigation. We chose to complete treatment with a further four cycles of mFOLFIRINOX after surgery, for maximal systemic effect within the bounds of patient tolerance.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a proof-of-concept pilot study conducted at two academic centers in the USA. Eligible patients were required to have histologically confirmed adenocarcinoma of the head, body, or tail of the pancreas with variants such as squamous cell, acinar cell, spindle cell, or neuroendocrine cancer excluded. The cancer had to be classified as resectable according to National Comprehensive Cancer Network (NCCN) criteria by demonstrating: (i) a patent superior mesenteric/portal vein confluence (either absence of involvement or 180 degrees of abutment with no vein contour irregularity); (ii) a definable tissue plane between the tumor and regional arterial structures including the celiac axis, common hepatic artery, and superior mesenteric artery; and (iii) no evidence of metastases on triple phase CT imaging. Radiographic confirmation of resectability had to be established at a multidisciplinary conference that included at least one experienced pancreatic surgeon, one radiologist, and one medical oncologist. Patients could not have had any prior treatment for pancreatic cancer and were required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. Other inclusion criteria were age >21 years, no currently active second malignancy, no history of cerebrovascular accident or myocardial infarction within 6 months and a negative pregnancy test with agreement to birth control methods in females of reproductive age. Lab values had to be in the following range:

granulocytes $>1500/\mu\text{L}$; Platelets $>100\,000/\mu\text{L}$; Total bilirubin $1.5 \times \text{ULN}$; SGOT/SGPT $2.5 \times \text{ULN}$; Serum Creatinine 1.5 mg/dL . All patients provided both oral and written informed consent. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board at both participating medical centers.

2.2 | Procedures

Patients meeting all eligibility criteria received mFOLFIRINOX (oxaliplatin 85 mg/m^2 IV over 2 h and then leucovorin 400 mg/m^2 over 2 h immediately following oxaliplatin; irinotecan 180 mg/m^2 was administered over 90–120 min via a Y connector during the infusion of leucovorin; 5FU 2400 mg/m^2 was then administered via an ambulatory pump as a 46 h continuous infusion; peg-filgrastim 6 mg was given subcutaneously on day 3) every 2 weeks in the outpatient clinic, providing that they met protocol criteria. Formal toxicity assessment was performed prior to each treatment, with appropriate dose modifications per protocol. Four cycles of mFOLFIRINOX were given prior to reassessment of tumor status via triple phase CT imaging of the chest, abdomen and pelvis, or magnetic resonance cholangiopancreatography (MRCP) with CXR if CT could not be done. Response was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), and adjudged to be complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). If the imaging did not show progression to unresectable status or interval development of radiographic metastases, patients with an adequate performance status underwent surgical exploration. This consisted of diagnostic laparoscopy followed by either pylorus-preserving pancreaticoduodenectomy or pancreaticoduodenectomy (for tumors in the head/neck/uncinate process) or distal pancreatectomy and splenectomy (for lesions in the body/tail). A patient deemed unresectable at the time of surgery was removed from the study and offered alternative therapy at the treating team's discretion. If resection was performed, final margins were recorded as negative (R0) or positive (R1) for tumor. A margin was designated as positive if tumor cells were present at the inked SMA margin, the common bile/hepatic duct or the pancreatic transaction margins. The degree of pathologic response was assessed by the Evans criteria.²⁶ Patients were subsequently restarted on mFOLFIRINOX chemotherapy for up to four additional cycles (4–10 weeks after surgery depending on patient recovery) with assessment and dose adjustments as per the preoperative plan. A final staging evaluation was then performed with CT or MRCP plus CXR, blood tests and physical examination. If a patient remained in clinical remission he/she was switched to surveillance with follow-up according to standard NCCN guidelines. Patients were to be followed for 5 years after completion of study or until death, whichever occurred first, with visits every 3 months for years 1 and 2 and every 6 months for years 3–5.

Because surgery-related deaths after PST were of concern, there was close monitoring of this adverse event. Specifically, a stopping rule developed by Goldman²⁷ was used as a guide for early termination due to surgery-related deaths. The stopping rule required that early termination be considered if three deaths occurred in the first fourteen or fewer patients or four deaths in the first thirty-one or fewer patients. Additionally, febrile neutropenia, platelet counts less than $20 \times 10^3/\mu\text{L}$, and diarrhea requiring hospitalization were also closely monitored. A stopping rule, based on an acceptable level of 10% and upper limit of

20%, required that early termination be considered if four such adverse events occurred in the first four patients, five such adverse events in the first ten or fewer patients, six such adverse events in the first seventeen or fewer patients, or seven such adverse events in the first twenty-four or fewer patients. The study was monitored by an independent Data and Safety Monitoring Board (DSMB), consisting of two independent medical oncologists, the data manager, the study statistician and a pharmacist, which met monthly to review patient enrollment, serious or unexpected adverse events, those events pertinent to the stopping rules, and any delay in time to surgery or delayed wound healing. Annual non-blinded safety reports, including all serious adverse events, were provided to the IRB.

2.3 | Outcomes

The primary outcome was the percentage of patients completing preoperative mFOLFIRINOX chemotherapy and subsequent pancreatic resection. Secondary outcomes were the percentage of patients completing all therapy, including four cycles of preoperative mFOLFIRINOX, successful pancreatic resection and four cycles of postoperative mFOLFIRINOX; the percentage of patients experiencing treatment related toxicity; the R0 resection rate for all patients entering the study and for all patients completing surgery; progression free survival (PFS) (defined as time from the start of study treatment until time of progression or death, whichever occurs first) and overall survival (OS) (defined as time from the start of study treatment until death from any cause). Adverse events were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) and were assessed from enrollment to 30 days after completion of the final cycle of postoperative mFOLFIRINOX chemotherapy, or 30 days after completion of the final therapeutic intervention, if patients terminated their therapy early per protocol.

2.4 | Statistical analysis

This pilot study was conducted using a single-stage design to detect a minimum primary endpoint success rate of 75%, compared with 50% which was considered reasonable in this setting, using a one-sided alpha of 0.15. Twenty-one patients were to be enrolled. If thirteen or fewer patients met the criteria for success, the regimen would not be considered worthy of additional evaluation. This design yields at least 0.85 probability of a positive result if the true success rate is at least 75% and at least 0.90 probability of a negative result if the true success rate is at most 50%. Data were summarized using descriptive statistics. Point estimates and 95% confidence intervals (CI) were computed for binary endpoints. The Kaplan-Meier method was used to estimate patient's progression free survival (PFS) and overall survival (OS). The log-rank test was used to compare PFS and OS between resection and no resection groups. All analyses were conducted using SAS 9.4 software (SAS Inc., Cary, NC).

2.5 | Role of the funding source

As this pilot study was unfunded there were no potential conflicts of interest.

3 | RESULTS

Twenty-one patients were enrolled between February 4, 2013 and February 9, 2015 as per study design, and all twenty-one patients were included in the analysis. Data lock was February 10, 2017. Figure 1 shows the CONSORT diagram of the study. The baseline characteristics of the twenty-one patients are shown in Table 1. All enrolled patients initiated therapy, with a median age of 62 (47–78), and with 76% ECOG 0, and 24% ECOG 1. Median pretherapy CA 19-9 was 68 U/mL (<1-1058) and median tumor size was 30 mm (18–63). Twenty/twenty-one patients (95%) completed all four cycles of preoperative mFOLFIRINOX; one patient withdrew for toxicity (Grade 3 nausea and vomiting, fatigue) and has no follow up and survival data. This patient was excluded from the survival analysis.

Table 2 summarizes the treatment results. Radiographic response, as judged by RECIST criteria, was 1 CR, 3 PR, and 16 SD for the 20 patients completing chemotherapy. Twenty/twenty-one patients underwent exploration with intent to resect; three patients were found to have metastatic disease in the liver not seen on preoperative imaging and were deemed unresectable. Seventeen/twenty-one (81%) underwent pancreatic resection (head 14/17, body 2/2, tail 1/2). Sixteen/seventeen (94%) of those resected had an R0 resection (16/21 [76%] intention to treat [ITT]) with 10/17 (59%) showing evidence of treatment effect (grade II and III as judged by Evans criteria) with one pathologic CR. After the completion of four cycles of preoperative mFOLFIRINOX, the median tumor size and CA 19-9 were reduced from 30 to 22 mm ($P = 0.26$) and from 68 to 31U/mL ($P = 0.09$), respectively. Fourteen/seventeen (82%) (14/21 [67%] ITT) patients completed four cycles of postoperative mFOLFIRINOX. Two patients died within 90 days of surgery and did not start adjuvant therapy (see below), and one patient was withdrawn per protocol after one cycle owing to grade 4 neutropenia.

Table 3 summarizes the adverse events. The most common adverse events were diarrhea, anorexia, and fatigue. Grade 4 adverse events were rare, with one event (hypokalemia) preoperatively, and one event (neutropenia) postoperatively. Grade 3 events were more common, but none exceeded 5% of treatment cycles other than diarrhea (6% cycles preoperatively and 7% cycles postoperatively), anorexia and fatigue (9.6% and 5.7% cycles postoperatively, respectively). Dose modifications were required in 30% of patients preoperatively (neuropathy 1; thrombocytopenia 2; neutropenia 3; diarrhea 2) and in 26% of patients postoperatively (neuropathy 3; diarrhea 3; allergic reaction 1) (overlapping toxicities in some patients).

Table 4 summarizes the survival and disease progression/recurrence endpoints. As of the date of data lock, the median follow up was 27.7 (3.1–47.1) months. Two patients died within 90 days of surgery (one from an acute MI, 14 days postop; one from uncontrolled arterial hemorrhage, 19 days postop) and one stopped therapy per protocol following cycle 1 of postoperative therapy (Grade 4 neutropenia following two dose reductions). Overall, eleven patients have died, five are alive without recurrence (48, 44, 35, 33, 15 months), four are alive with recurrence (45, 40, 37, 25 months) and one withdrew from the study with no follow up data. CA 19-9 is often cited as predictive of outcome. No patient currently alive and disease free had a value >45 U/mL immediately prior to surgery (1 non-expressor) with

all 4 such patients with low initial values (<1-261). Only one of four of those alive with disease had a preoperative value <45 U/mL although all had a notable decline. Five of ten of those who died could not achieve this value (one non-expresser).

The median OS for the twenty patients who completed PST and underwent surgical exploration was 34 months (95% CI 12.3–57.6) (Figure 2A) with PFS rate at 24 months of 0.27 (95% CI 0.10–0.47) (Figure 2B). Patients whose disease was resected had a longer overall survival than unresectable patients ($P = 0.0014$), with a median OS of 35.5 months (95% CI 15–59.2) vs 10.1 months (95% CI 7.9–12.3), respectively (Figure 2C). The patients with resectable cancers also had a significantly higher PFS rate at 24 months than those with unresectable disease ($P < 0.0001$), 0.31 (95% CI 0.11–0.54) vs 0, respectively (Figure 2D).

4 | DISCUSSION

This study was designed to determine whether PST, using four cycles of mFOLFIRINOX, was both feasible and tolerable in patients with resectable pancreatic cancer and ECOG PS of 0 or 1, and would not compromise an acceptable R0 resection rate. 95% of patients completed all planned PST and were deemed operable, with 81% able to undergo pancreatic resection with an R0 of 94%, thus meeting the primary endpoint of this study. A number of pertinent observations can be made.

First, the modification of FOLFIRINOX used in this study²⁵ is more tolerable than the original regimen²³ and facilitates completion of therapy with acceptable toxicity. This tolerability means that future studies will likely be able to use up to eight cycles of therapy, or more, as deemed necessary for optimal results. The current SWOG 1505 Intergroup study, which randomizes patients with potentially resectable pancreatic cancer to mFOLFIRINOX versus gemcitabine plus nab-paclitaxel, before and after surgery, uses a total of six cycles preoperatively. A parallel ALLIANCE/Intergroup study A021501, in borderline resectable pancreatic cancer, uses eight cycles of mFOL-FIRINOX versus seven cycles followed by stereotactic radiation. These studies will provide additional toxicity data. We chose to include only those patients with ECOG PS of 0 or 1, as in previous studies exploring a neoadjuvant approach, as these individuals would be expected to be healthy enough to undergo surgery and potentially to complete the PST. Future studies could consider the inclusion of patients with a less robust PS, depending on goals of therapy and intensity of the proposed treatment.

Second, the ability to perform pancreatic resection is not compromised by a primary systemic approach, with resection rates at least as good as those of immediate surgery. The R0 resection rate was excellent (94% of those actually resected, and 76% of patients by intention to treat) and the fact that more than 50% of specimens showed treatment effect with one pathologic CR was encouraging. The reported margin negative resection rate in patients taken to surgery with or without some form of presurgical therapy is highly variable (17–90%), depending to a large extent on the definitions and methods used. A recent comprehensive review highlights the different methodologies employed, the results, and the controversies surrounding this topic.²⁸

Thirdly, there was no detectable radiographic or serologic evidence of disease progression while on chemotherapy, within the current limitations of these tests. The actual radiographic response of 20% (1 CR and 3 PR by RECIST) is gratifying and comparable with the best results seen to date. A systematic, well controlled study performed at MD Anderson Cancer Center found an overall 12% response rate in patients with borderline resectable disease receiving neoadjuvant therapy²⁹ and a recent meta-analysis of the literature determined a 14.6% response rate in resectable disease.³⁰ Prior experience suggests that the three patients found to be inoperable at the time of surgery, owing to occult liver metastases, almost certainly had biologically aggressive disease unresponsive to chemotherapy, and would likely have been inoperable a priori or would have recurred shortly after surgery. Diagnostic laparoscopy prior to any therapy, either PST or surgery, could be helpful in identifying additional individuals with occult metastatic disease at the time of diagnosis and should potentially be used in all future studies.³

Two patients died in the perioperative period. The first, who suffered a myocardial infarction, was a young man recovering well from surgery who had undetected cardiovascular disease leading to his death. The second patient had profound bleeding from a vascular graft between the aorta and the hepatic artery (which was inadvertently injured during resection). The contribution of chemotherapy to either one, or both, of these deaths is unlikely but possible.

Third, most eligible patients completed all planned post-surgical mFOLFIRINOX, if the two patients with peri-surgical deaths are censured, with 93% able to do so (66% of all registered patients). We were concerned that this intensive regimen could be a problem following surgery, but toxicity postoperatively was no worse than preoperatively. Dose adjustments were made as needed to account for individual tolerance. It is noteworthy that the completion rate of single agent gemcitabine (the previous standard of care) in all comers in this setting is suboptimal at 62%.¹⁵ Currently the PRODIGE24/AC-CORD24 study is evaluating the use of mFOLFIRINOX versus gemcitabine in the postoperative setting and this will provide more data on the relative tolerability and efficacy of these regimens following surgery. The Alliance/Intergroup A021101 study of perioperative therapy in borderline resectable disease also used four cycles of mFOLFIRINOX in the preoperative setting, but switched to gemcitabine only following surgery; the completion rate of all planned therapy was 41%.³¹

The limitations of this study include the necessarily small sample size of a pilot study, inclusion of patients with PS of ECOG 0 or 1 only, the limited number of participating institutions and the fact that more than one pathologist and radiologist reviewed results. In addition, one patient chose to discontinue her participation in the study and was lost to follow up, such that she could not be included in the analysis of PFS and OS. The strengths include the quality control, with each patient reviewed at a multi-disciplinary pancreaticobiliary conference prior to enrollment and at each critical step, the experience of the pancreatic surgeons and medical oncologists, the median duration of follow up of 27.7 months and the close adherence to protocol criteria and guidelines.

5 | CONCLUSIONS

Based on the results of this study, and in view of similar results with the identical regimen in the Alliance/Intergroup A021101 study in borderline resectable disease,³¹ the feasibility and potential utility of mFOLFIRINOX as primary systemic therapy for resectable pancreatic cancer is supported. The American Society of Clinical Oncology (ASCO) Clinical Practice guidelines now recommend this type of approach when there are unfavorable findings based on anatomic criteria, clinical performance status or CA 19-9 levels, and suggest that it be offered as an alternative treatment strategy to immediate resection in all other cases.³² As the results of the many ongoing studies in this setting are reported, this recommendation could be modified or extended. Alternatives such as gemcitabine plus nab-paclitaxel, or investigational regimens incorporating novel agents such as targeted drugs or immunotherapy, may also be considered as appropriate in this highly lethal disease. Response modified therapy guided by advanced imaging, relevant blood tests such as CA 19-9, circulating tumor cells and/or cell free DNA and laparoscopy, could take this a step further, with the duration and type of PST determined by response rather than tied to a fixed number of cycles of one regimen. The optimal integration of other regional treatments such as Stereotactic Body Radiation Therapy (SBRT)³³ and irreversible electroporation³⁴ has yet to be determined and will require additional study.

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FIGURE 1.
CONSORT diagram

FIGURE 2.

Kaplan-Meier survival curves. OS, overall survival; PFS, progression free survival

TABLE 1

Demographic and clinical characteristics of 21 patients at study entry

Characteristics	N (%)
Age, median (range), years	62 (47–78)
Sex	
Male	13 (62)
Female	8 (38)
Race	
White	20 (95)
Black	1 (5)
Performance status (ECOG)	
0	16 (76)
1	5 (24)
Tumor location	
Head	17 (80)
Body	2 (10)
Tail	2 (10)
Tumor size, median (range), mm	30 (18–63)
CA 19-9, median (range), U/mL	68 (<1-5058)

TABLE 2

Summary of the treatment results

Characteristics	N (%)
Preoperative mFOLFIRINOX treatment	
4 cycles	20 (95)
<4 cycles	1 (5)
Radiographic response	
CR	1 (5)
PR	3 (14)
Stable disease	16 (76)
Unknown	1 (5)
Surgical resection	
Yes	17 (81)
No	4 (19)
Pathologic response	
R0 resection	16/17 (94)
Treatment effect present	10 (48)
No treatment effect present	6 (28)
Unknown treatment effect ^a	5 (24)
Tumor size before mFOLFIRINOX treatment, median (range), mm	30 (18–63)
Tumor size after cycle 4 of mFOLFIRINOX treatment, median (range), mm	22 (0–72)
CA 19-9 before mFOLFIRINOX treatment, median (range), U/mL	68 (1-5058)
CA 19-9 after cycle 4 of mFOLFIRINOX treatment, median (range), U/mL	31 (1-295)
Postoperative mFOLFIRINOX treatment (<i>n</i> = 17)	
4 cycles	14 (82)
<4 cycles	3 (18)

^aThree of the patients with unknown treatment effect did not have surgery due to metastatic disease; one withdrew, and one did not report.

TABLE 3

Summary of adverse events per treatment cycles

Adverse events	Preoperative (total 82 cycles given)		Postoperative (total 57 cycles given)	
	Grade 3 (%)	Grade 4/5 (%)	Grade 3 (%)	Grade 4/5 (%)
Hematology				
Neutropenia	3 (3.6)			1
Febrile neutropenia	2 (2.4)			
Thrombocytopenia	1 (1.2)			
Gastrointestinal				
Diarrhea	5 (6.0)		4 (7.0)	
Anorexia			5 (9.6)	
Nausea	2 (2.4)			
Vomiting	1 (1.2)			
Metabolism				
Hyperglycemia	2 (2.4)		2 (3.8)	
Increased bilirubin	1 (1.2)			
Hyponatremia	3 (3.6)			
Hypokalemia	1 (1.2)	1 (1.2)	1 (1.9)	
Increased SGPT	3 (3.6)			
Systemic				
Death				2 pretherapy
Fatigue	3 (3.6)		3 (5.7)	
Infection	1 (1.2)		2 (3.8)	
Thrombosis			1 (1.9)	
Weight loss			2 (3.8)	
Peripheral neuropathy			2 (3.8)	

TABLE 4

Summary of survival and disease progression/recurrence end points

End point	Event	No. of patients	No. of events	Overall event rate (%)	Event-free survival rate (95% CI)		Median survival time (mo) (95% CI)
					At 12 mo	At 24 mo	
90 days mortality							
Patients completed primary systemic therapy and go to surgery	Death from any cause	20	2	10	-	-	-
	Patients went to surgery and had resection	17	2	12	-	-	-
	Patients went to surgery and had no resection	3	0	0	-	-	-
Overall survival							
Patients completed primary systemic therapy and go to surgery	Death from any cause	20	11	55	0.80 (0.55–0.92)	0.60 (0.36–0.78)	34 (12.3–57.6)
	Patients went to surgery and had resection	17	8	47	0.88 (0.61–0.97)	0.71 (0.43–0.87)	35.5 (15–59.2)
	Patients went to surgery and had no resection	3	3	100	0.33 (0.1200.55)	0	10.1 (7.9–12.3)
Progression-free survival							
Patients completed primary systemic therapy and go to surgery	Progression during preoperative treatment, recurrence after surgery, or death from any cause	20	14	60	0.53 (0.29–0.72)	0.27 (0.10–0.47)	12.8 (8.8–19.2)
	Patients went to surgery and had resection	17	11	65	0.63 (0.35–0.81)	0.31 (0.11–0.54)	15.2 (10.5–24.1)
	Patients went to surgery and had no resection	3	3	100	0	0	2.8 (2.6–3.7)