**Neoadjuvant FOLFIRINOX Application in Borderline Resectable Pancreatic Adenocarcinoma**

*A Retrospective Cohort Study*

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**Abstract:** 5-Fluorouracil, oxaliplatin, irinotecan, and leucovorin (FOLFIRINOX) has not been extensively used in the neoadjuvant setting because of concerns with safety and toxicity. We evaluated our institutional experience with neoadjuvant FOLFIRINOX in borderline resectable pancreatic adenocarcinoma (BRPAC). The primary endpoints were completion of therapy to surgery and negative resection margin (R0) rate.

Patients with BRPAC treated with neoadjuvant FOLFIRINOX were retrospectively analyzed. Between August 2011 and September 2013, 20 patients with BRPAC treated with neoadjuvant FOLFIRINOX were identified. Most patients (88.8%) completed FOLFIRINOX therapy and underwent resection. Abutment of venous structures was identified in 13 cases (72.2%), while short segment portal vein encasement in 3 cases (16.6%). Isolated superior mesenteric artery abutment was identified in 2 cases (11.2%). Patients received a median of 4 cycles of FOLFIRINOX. There was 1 case of progression. Vascular resection was performed in 9 cases (44%). All patients underwent margin negative resection (R0). Neoadjuvant FOLFIRINOX was generally safe and the expected toxicity did not prevent surgery allowing for a high rate of R0 resection.

**INTRODUCTION**

As the incidence of pancreatic cancer continues to increase, the mortality rate remains relatively unchanged. The American Cancer Society estimates that approximately 46,420 people will be diagnosed with pancreatic cancer in 2014 and of these, 39,590 will die from this disease. This generally grim prognosis accentuates the quest to identify new treatment strategies for pancreatic adenocarcinoma (PADC).

Surgical resection with chemotherapy (usually adjuvant) remains the only potentially curative approach, offering an actuarial survival rate of about 20% at 5 years. Unfortunately, the majority of patients present with metastatic disease, precluding any surgical intervention and leading to an estimated survival of 2% at 5 years for all comers. Approximately, 10% of newly diagnosed pancreatic cancers present with clearly resectable localized disease and approximately 40% of patients present with locally advanced or borderline resectable disease.

Negative margin status (R0 resection) is among the strongest predictors for long-term survival in pancreatic cancer and remains the goal of a curative intent resection. Consensus statements have been developed to guide the classification of pancreatic tumors based on the likelihood of achieving a margin negative resection. The National Comprehensive Cancer Network (NCCN) consensus statement defines PADC as resectable, borderline resectable, and unresectable (Table 1). Borderline resectable lesions represent a particular challenge as, although potentially resectable, they carry a high likelihood of incomplete resection because of involvement of vital structures. The rate of microscopic positive resection margins (R1) reported in the literature varies enormously between 16% and 75% of cases. The wide range is in part secondary to inconsistencies in the pathology review of pancreatic resection specimens. Prior studies indicate that, in perhaps a third of the cases, neoadjuvant therapy could potentially improve resectability of locally advanced tumors.

The enthusiasm surrounding the results of the Actions Concertées dans les Cancers Colo-Rectaux et Digestifs (ACCORD) 11 trial, showing improved survival with FOLFIRINOX (5-fluorouracile [FU], oxaliplatin, irinotecan, and
leucovorin) in metastatic PADC,13 prompted several authors to study the effect of neoadjuvant FOLFIRINOX in locally advanced PADCs. Many of these small pilot studies were conducted on a mixed cohort of borderline resectable and locally advanced unresectable tumors. To our knowledge, Christians et al14 were the first to report on the use of neoadjuvantly treated locally advanced unresectable tumors. To our knowledge, conducted on a mixed cohort of borderline resectable and advanced PADCs. Many of these small pilot studies were study the effect of neoadjuvant FOLFIRINOX in locally resection rates. study were completion of therapy to surgery and R0 table toxicity and resection rate. The primary endpoints of this neoadjuvant agent in borderline resectable tumor with accep- patients with BRPAC. Our hypothesis is that FOLFIRINOX can be used as neoadjuvant agent in borderline resectable tumor with accept- able toxicity and resection rate. The primary endpoints of this study were completion of therapy to surgery and R0 resection rates.

**METHODS**

A retrospective review of the University of Colorado, Aurora, CO, pancreatic database was conducted between August 2011 and September 2013. The study was approved by the Internal Review Board of the University of Colorado. Treatment-naı¨ve patients, diagnosed with BRPAC, who received neoadjuvant FOLFIRINOX chemotherapy with or without chemoradiation, were identified. All patients were presented at a multidisciplinary tumor board and all diagnostic images were carefully reviewed by expert pancreatic surgeons and radiologists. Each patient had at least 2 multiphasic pancreatic protocol computed tomographies (CTs) available in his/ her records. The CT imaging obtained at the time of PADC diagnosis was reviewed and utilized to confirm the presence of BRPAC.

Borderline resectability was defined according to the NCCN.9 The definition includes radiologic findings of venous involvement of the superior mesenteric vein (SMV) or portal vein (PV) with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximally and distally, allowing for safe resection and reconstruction. As for arterial involvement, radiologic findings of encasement of a short segment of the hepatic artery, without evidence of tumor extension to the celiac axis and/or tumor abutment of the superior mesenteric artery involving ≤180° of the arterial circumference were considered BRPAC. Neoadjuvant FOLFIRINOX chemotherapy was generally administered following the doses and intervals described by the ACCORD 11 trial. Patients with a biopsy- proven diagnosis of PADC, with acceptable performance status as defined by an Eastern Cooperative Oncology Group (ECOG) of 0 or 1, were initially selected to undergo 4 cycles of FOLFIRINOX. A typical cycle consists of oxaliplatin, 85 mg/m²; irinotecan, 180 mg/m²; leucovorin, 400 mg/m²; and FU, 400 mg/m² bolus followed by 2400 mg/m² 46-hour continuous infusion, once every 2 weeks. Adverse events during treatment were evaluated according to the Common Terminology Criteria for Adverse Events.15 Treatment effects were evaluated by an abdominal multiphasic pancreatic protocol CT following completion of neoadjuvant chemotherapy, or in the case of excessive toxicities, soon after interruption of treatment. Patients who demonstrated tumor response proceeded to curative intent surgical resection. Patients who did not show response to neoadjuvant chemotherapeutic treatment were offered neoadjuvant chemoradiation treatment unless otherwise chosen by the treating physician or by the patient.

The treating oncologist based on patient tolerance of the therapy, adjusted the chemotherapeutic regimen accordingly. The CT imaging immediately obtained preceding definitive surgical intervention was identified in the patient record and utilized to assess disease response to treatment. In this study, the authors did not utilize the Response Evaluation Criteria in Solid Tumors (RECIST) to guide the radiographic assessment of tumor burden, as the size of the tumor was not the only determinant of disease progression or response to treatment. In addition, Katz et al16 have shown that radiographic down-staging is rare after neoadjuvant chemotherapy and concluded that the RECIST criteria are inadequate in the evaluation of patients with BRPAC. For the purpose of this study, we focused on identifying changes in the anatomic relationship between the tumor and the surrounding vascular structures (mainly progression of vascular involvement) and evidence of new unequivocal metastatic disease.

Treatment effect was evaluated according to a categorical scale including stable disease, any subjective response to treat- ment, and disease progression. Stable disease was characterized...
by absence of substantial changes from diagnostic imaging or evidence of distant disease. Response to treatment was characterized by decrease in vessel involvement (artery and/or vein) or new evidence of fat plane between tumor and vital anatomic structure that was felt to improve the chances of a successful surgical resection. Disease progression was characterized by progression of vessel involvement and/or evidence of distant disease. The histologic grade of treatment response was assessed by a trained gastrointestinal pathologist on permanent sections of the surgical specimen and graded according to the College of American Pathologists scheme (Table 2).17

The primary endpoints for this analysis were completion of therapy to surgery, and R0 resection rate, defined as the absence of microscopic evidence of tumor within at least 1 mm from the surgical resection margins. Beginning in 2011, our institutional protocol for evaluation of surgical margins included bile duct, pancreatic duct, uncinate, retroperitoneal, and vascular groove according to the procedure performed. Patients receiving at least 1 cycle of FOLFIRINOX were included in the analysis. Progression-free survival (PFS) indicates the interval, in months, between the first cycle of neoadjuvant FOLFIRINOX and evidence of disease recurrence or progression as assessed by radiographic imaging (local or metastatic), surgical exploration, or death. Follow-up information were obtained from clinic visit records, communication with primary care physicians, or national death registry. Overall survival (OS) indicates the interval between the first cycle of chemotherapy and the occurrence of death from any cause. Patients without disease recurrence at the time of last contact were censored. The Kaplan–Meier method with a 2-sided 95% confidence interval (CI) based on Greenwood’s variance was applied for the estimation of PFS and OS. The available data were summarized using descriptive statistics.

RESULTS

Between August 2011 and September 2013, a total of 336 patients with PADC were evaluated and of these, 31 (9.2%) presented with BRPAC. Neoadjuvant treatment was offered to the entire cohort of BRPAC; however, 2 patients refused treatment and elected to proceed with primary surgical resection and 9 patients were offered gemcitabine in light of poor performance status (ECOG 2). The remaining 20 chemotherapy-naïve patients diagnosed with BRPAC were treated with neoadjuvant FOLFIRINOX. Two patients established care in a different state during treatment and were eventually lost to follow-up and therefore excluded from the analysis (Figure 1). A total of 18 patients remained available for final data analysis (Table 3). One patient experienced a significant adverse event (5-FU-associated coronary vasospasm with elevated troponin level) during the administration of the first cycle of FOLFIRINOX. The patient required treatment interruption and was eventually transitioned to gemcitabine. Median age at diagnosis was 65 years (range: 58–68 years) with 10 males (55.6%) and 8 females (44.4%). Pancreatic head adenocarcinoma was

TABLE 2. Histopathological Grade of Tumor Response to Neoadjuvant Treatment

| Grade | Criteria                                      |
|-------|-----------------------------------------------|
| 0     | No residual tumor (complete response)        |
| 1     | Minimal residual cancer (marked response)    |
| 2     | Moderate response                             |
| 3     | Poor or no response (no definitive response identified) |

Adapted from the College of American Pathologists scheme.

FIGURE 1. Distribution of PADC between July 2011 and August 2013 based on resectability and treatment allocation. PADC = pancreatic adenocarcinoma.
identified in 10 patients (61.1%) representing the most common anatomic tumor location. Abutment of venous vessels (PV/SMV) was present in 13 patients (72.2%) and represented the leading determinant for borderline resectability followed by short segment encasement of venous vessels in 3 patients (16.8%). Determinants for borderline resectability are summarized in Table 4. Overall, a total of 74 cycles of chemotherapy were administered with a median of 4 cycles of FOLFIRINOX per patient (range: 3–5 cycles). Three patients (16.7%) received only 2 cycles prior to operative intervention and 3 patients (16.7%) received >6 cycles prior to definitive surgical intervention. A total of 10 patients (55.6%) experienced grade 3 or 4 toxicities during treatment; the most common adverse events were anorexia (n = 3; 16.7%), nausea/vomiting (n = 2; 11.1%), and peripheral neuropathy (n = 4; 22.2%). Adverse events during treatment required hospitalization in 3 patients (16.7%), including 1 patient who developed neutropenic fever. Neoadjuvant chemoradiation was offered to 8 patients (44.4%) of whom 5 eventually had radiographic response (Table 5). Two patients, with no evidence of response to neoadjuvant chemotherapy, proceeded straight to surgery without chemoradiation treatment. In one case, this was dictated by patient preference to avoid chemoradiation treatment and intention to proceed directly to surgical intervention. In the second case, the treating surgeon decided to directly proceed to surgical intervention. Median interval from the date of first FOLFIRINOX cycle to definitive surgical treatment was 4 months (range: 2–4 months). One patient experienced disease progression (biopsy proven liver metastasis) 7 months after the first dose of chemotherapy. At that time, he had received 6 doses of neoadjuvant FOLFIRINOX and completed neoadjuvant chemoradiation. Treatment response via multiphasic pancreatic protocol CT was carefully evaluated in all patients prior to surgical intervention at a median of 2.5 months (range: 1–4 months) from first administered dose of FOLFIRINOX. We observed some evidence of radiographic disease response in 7 patients (41.2%) and stable disease in the remaining 10 patients (55.6%). In particular, 4 patients (22.1%) experienced complete resolution of venous involvement (Table 4). A Whipple procedure was performed in 12 cases (70.6%), distal pancreatectomy in 4 cases (23.5%), and 1 case (5.6%) required total pancreatectomy. Vascular resection with reconstruction was performed in 9 cases (52.9%) with tumor involvement of the superior mesenteric artery, SMV and PV abutment (27.8%) and 1 case (5.6%) required total pancreatectomy. Vascular resection with reconstruction was performed in 9 cases (52.9%) with tumor involvement of the superior mesenteric artery, SMV and PV abutment (27.8%) and 1 case (5.6%) required total pancreatectomy. Vascular resection with reconstruction was performed in 9 cases (52.9%) with tumor involvement of the superior mesenteric artery, SMV and PV abutment (27.8%) and 1 case (5.6%) required total pancreatectomy.

### Table 3. Patients and Surgical Characteristics, n = 18

| Characteristics                  | N (%)  |
|----------------------------------|--------|
| Age, y                           | 65     |
| Median                           |        |
| Range (58–68)                    |        |
| Gender                           |        |
| Male                             | 10 (55.6) |
| Female                           | 8 (44.4)  |
| ECOG                             |        |
| 0                                | 9 (50)  |
| 1                                | 9 (50)  |
| Tumor location                   |        |
| Head                             | 11 (61.1) |
| Uncinate                         | 1 (5.6)  |
| Body                             | 4 (22.1)  |
| Tail                             | 1 (5.6)  |
| Head and tail                    | 1 (5.6)  |
| Surgical procedure               |        |
| Whipple                          | 12 (70.6) |
| Distal pancreatectomy            | 4 (23.5)  |
| Total pancreatectomy             | 1 (5.9)  |
| Vein resection                   |        |
| Performed                        | 9 (52.9) |
| NotPerformed                     | 8 (47.1) |
| Surgical margins                 |        |
| Negative (R0)                    | 17 (100) |
| Lymph nodes removed              |        |
| Median                           | 19     |
| Range (16–25)                    |        |
| Lymph nodes status               |        |
| Negative                         | 7 (41.2) |
| Positive                         | 10 (58.8) |
| Lymphovascular invasion          |        |
| Negative                         | 7 (41.2) |
| Positive                         | 10 (58.8) |
| Perineural invasion              |        |
| Positive                         | 12 (70.6) |
| Hospital LOS, d                  |        |
| Median                           | 9      |
| Range (8–10)                     |        |
| Postoperative complications      |        |
| DGE                              | 4 (23.5) |
| SSI                              | 3 (17.6) |
| Chyle leak                       | 2 (11.8) |

Surgical characteristics and postoperative complications refer to n = 17 patients. DGE = delayed gastric emptying, ECOG = Eastern Cooperative Oncology Group, LOS = length of hospital stay, SSI = surgical site infection.

### Table 4. Characteristics of Borderline Resectable Tumor by Vessel Involvement Neoadjuvant and Postneoadjuvant Treatment, Assessed by CT Imaging, n = 18

| Characteristics                  | Pretreatment, N (%) | Posttreatment, N (%) |
|----------------------------------|---------------------|----------------------|
| Isolated venous involvement      | 4 (22.2)            | 0                    |
| PV abutment                       | 5 (27.8)            | 0                    |
| SMV abutment                      | 3 (16.6)            | 1 (5.6)              |
| PV/SMV abutment                   | 3 (16.6)            | 2 (11)               |
| PV encased (short segment)        | 1 (5.6)             | 0                    |
| PV/SMV encased                   | 1 (5.6)             | 1 (5.6)              |
| Isolated arterial involvement     | 2 (11)              | 2 (11)               |
| SMA abutment                      | 1 (5.6)             | 1 (5.6)              |
| Synchronous arterial and venous involvement | 1 (5.6) | 1 (5.6) |
| HA and PV abutment                | 1 (5.6)             | 1 (5.6)              |
| CAX and PV abutment               | 1 (5.6)             | 1 (5.6)              |
| SMA and PV encased (short segment) | 1 (5.6)            | 1 (5.6)              |
| Disease progression               | 0                   | 1 (5.6)              |

CAx = celiac axis, HA = hepatic artery, PV = portal vein, SMA = superior mesenteric artery, SMV = superior mesenteric vein.
specimens revealed complete tumor response in 1 patient (5.9%), evidence of partial response in 9 patients (52.9%), and poor or no response in 7 patients (41.2%) (Table 5). The median length of hospital stay was 9 days (range 8–10). There were no perioperative or in-hospital deaths attributable to the surgical procedure. The main postoperative complications were delayed gastric emptying in 4 patients (23.5%), surgical site infections in 3 patients (17.6%), and chyle leak in 2 patients (11.8%). None of the patients required hospital admission following surgical intervention and their complications were managed in our surgery clinic. The median follow-up from the date of first administered dose of FOLFIRINOX was 14.5 months (range: 10–17 months). The Kaplan–Meier estimated median PFS and OS were not reached because of the limited follow-up. For the entire cohort (n = 18), the 1-year PFS from first administered dose of FOLFIRINOX was 73.1% (95% CI: 43.1%–89.0%). We observed 4 (22.1%) local recurrences and 5 (27.8%) distant recurrences including the patient who experienced metastatic liver disease during the treatment (Figure 2). At a median of 17.5 months from the date of first administered dose of FOLFIRINOX, we observed 4 deaths with the earliest death occurring at 13 months and the latest at 25 months. The longest surviving patient is living 26 months from the first dose of chemotherapy without evidence of disease recurrence (Figure 4). Of the 18 patients treated with neoadjuvant FOLFIRINOX, 16 patients (88.9%) went on to receive adjuvant chemotherapy following resection. One patient refused adjuvant chemotherapy and 1 patient was still recovering from surgery at the time of this study. The only patient, who required treatment interruption and transition to neoadjuvant gemcitabine because of severe toxicity, eventually received 4 cycles of gemcitabine and underwent negative margin surgical resection. The patient is currently alive without evidence of disease recurrence. One patient who experienced complete histopathologic response to neoadjuvant treatment (including neoadjuvant FOLFIRINOX and neoadjuvant chemoradiation), eventually recurred with liver metastasis 4 months following surgical resection.

DISCUSSION

At the time the ACCORD 11 trial was reported, FOLFIRINOX represented the most significant improvement in OS for patients with metastatic pancreatic cancer and was associated with an overall 32% tumor response rate. However, its use as

| TABLE 5. Neoadjuvant Treatment Characteristics and Histopathological Tumor Response of Patients that Underwent Surgical Resection |
| --- |
| Characteristics | n (%) |
| FOLFIRINOX cycles |  |
| ≤2 | 3 (16.7) |
| 3–5 | 12 (66.6) |
| ≥6 | 3 (16.7) |
| Grade 3/4 toxicities |  |
| Neutropenia | 1 (5.6) |
| Neutropenic fever | 1 (5.6) |
| Anemia | 1 (5.6) |
| Thrombocytopenia | 2 (11.1) |
| Fatigue | 2 (11.1) |
| Mucositis | 1 (5.6) |
| Anorexia | 3 (16.7) |
| Nausea/vomiting | 2 (11.1) |
| Diarrhea | 3 (16.7) |
| Neuropathy | 4 (22.2) |
| Venous thrombosis | 1 (5.6) |
| Coronary vasospasm | 1 (5.6) |
| Hospitalization | 3 (16.7) |
| Neoadjuvant chemoradiation |  |
| Not administered | 10 (55.6) |
| Administered | 8 (44.4) |
| Histopathological tumor response |  |
| No residual tumor | 1 (5.6) |
| Minimal residual tumor | 4 (23.5) |
| Moderate response | 5 (29.4) |
| Poor/no response | 7 (41.2) |

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patients). Christians et al described their single-institutional cohort composed of locally advanced unresectable PADC. In their study, none of the patients had progression of disease during treatment; partial response was observed in 27.3% of the cases and stable disease in the remaining 72.7% of the cases. This limited study of patients treated with neoadjuvant FOLFIRINOX suggests that the majority of patients tolerated the therapy with expected toxicities and were able to undergo an R0 resection.

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CONCLUSION

This limited study of patients treated with neoadjuvant FOLFIRINOX for BRPAC suggests that the majority of patients tolerated the therapy with expected toxicities and were able to undergo an R0 resection.
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