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Original Article

Survival benefit of neoadjuvant FOLFIRINOX for patients with borderline resectable pancreatic cancer

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Backgrounds/Aims: While patients with borderline resectable pancreatic cancer (BRPC) are a target population for neoadjuvant chemotherapy (NAC), formal guidelines for neoadjuvant therapy are lacking. We assessed the perioperative and oncological outcomes in patients with BRPC undergoing NAC with FOLFIRINOX for patients undergoing upfront surgery (US).
Methods: The AHPBA criteria for borderline resectability and/or a CA19-9 level > 100 μ/mL defined borderline resectable tumors retrieved from a prospectively populated institutional registry from 2007 to 2020. The primary outcome was overall survival (OS) at 1 and 3 years. A Cox Proportional Hazard model based on intention to treat was used. A receiver–operator characteristics (ROC) curve was constructed to assess the discriminatory capability of the use of CA19-9 > 100 μ/mL to predict resectability and mortality.
Results: Forty BRPC patients underwent NAC, while 46 underwent US. The median OS with NAC was 19.8 months (interquartile range [IQR], 10.3–44.24) vs. 10.6 months (IQR, 6.37–17.6) with US. At 1 year, 70% of the NAC group and 41.3% of the US group survived (p = 0.008). At 3 years, 42.5 % of the NAC group and 10.9% of the US group survived (p = 0.001). NAC significantly reduced the hazard of death (adjusted hazard ratio, 0.20; 95% confidence interval, 0.07–0.54; p = 0.001). CA19-9 > 100 μ/mL showed poor discrimination in predicting mortality, but was a moderate predictor of resectability.
Conclusions: We found a survival benefit of NAC with FOLFIRINOX for BRPC. Greater pre-treatment of CA19-9 and multivessel involvement on initial imaging were associated with progression of the disease following NAC.

Key Words: Pancreatic cancer; Pancreatic neoplasms; Neoadjuvant therapy; CA-19-9 antigen

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease with a 5 year survival of 20% and expected increasing incidence in the coming years [1]. While surgical resection remains the only curative treatment modality, only 20% of patients have resectable disease at the time of presentation [2]. With the goals of downstaging locoregional disease, targeting micrometastatic systemic disease, and identifying patients who would likely benefit from surgical resection, patients with borderline resectable pancreatic cancer (BRPC) are targeted to receive neoadjuvant therapy, comprised of neoadjuvant chemotherapy (NAC) with either FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) or Gemcitabine-based treatment with or without chemoradiation therapy (CRT) [3]. The current literature suggests that for BRPC patients, NAC improves resection rate, R0 resection, and overall survival (OS), in comparison to upfront surgery (US) [3,4]. However, much of the evidence consists of retrospective analyses and a few randomized trials conducted with multiple different neoadjuvant treatment regimens [5-9]. Furthermore, despite international consensus on the definition of borderline resectability, much of the research, including RCTs, has variably defined BRPC either by anatomy or CA19-9 level, which makes the interpretation and application of these findings challenging [6,10-12]. As a result, there is a lack of consensus and formal guidelines regarding the specifics of neoadjuvant therapy for BRPC patients [9].

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We assessed the perioperative and oncological outcomes in patients with BRPC, defined by anatomy and/or CA19-9 level > 100 μ/mL, undergoing NAC with first line FOLFIRINOX to patients undergoing US, using retrospective and prospective data from a high-volume PDAC tertiary care center with a robust multidisciplinary team informing treatment decisions.

We hypothesized that there would be a survival benefit of NAC in patients with BRPC. Further, we hypothesized that our unique cut-off point of a CA19-9 level > 100 μ/mL to define borderline resectability would demonstrate good discriminatory capability in predicting disease resectability and mortality.

MATERIALS AND METHODS

Study design

This was an observational cohort analysis of patients included in an institutional data registry that was retrospectively collected between 2007 and 2017, and prospectively maintained from 2018 onwards. Our study period spanned 2007 through 2020.

Patient selection

This study involved human participants. The study was performed in line with the principles of the Declaration of Helsinki. Research Ethics Board (REB) approval was obtained from the Western University REB to conduct this study, for both the retrospective and prospective aspects. The REB Project Identification number is 110145. The Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri- Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940. Patients consented to inclusion in an institutional registry for research purposes.

We included in this study any patient with BRPC as defined by the AHPBA/SSO/SSAT/NCCN criteria for borderline resectability and/or a CA19-9 value > 100 μ/mL, a biochemical cut-off point uniquely used by our institution [2]. Patients were excluded if they underwent pancreaticoduodenectomy (PD) for an emergent or urgent indication, or if the pathology was uncertain at the time of treatment decision-making, thereby precluding them from consideration for NAC. CA19-9 was typically measured at the time of presentation, and was not routinely re-drawn after biliary decompression in the setting of obstructive jaundice. Previous studies have demonstrated minimal correlation between CA19-9 and total bilirubin, even in jaundiced patients [13-15]. Among patients in this study, CA19-9 and total bilirubin were weakly correlated (Spearman correlation coefficient = 0.22). As such, unadjusted CA19-9 values are presented.

Our institution began routinely recommending NAC for BRPC patients in 2018, while our institutional multidisciplinary tumor board began routinely recommending neoadjuvant therapy for BRPC patients in 2018. Thus, anyone who presented with BRPC prior to 2018 typically underwent US. Those who presented from 2018 onward were recommended to undergo neoadjuvant therapy. Accordingly, the patients in the US group serve as a historic comparison group. Those undergoing NAC were identified from the cohort of PDAC patients from 2018 onwards.

Treatment

At the time of the operative room (OR), patients whose disease was found to be resectable underwent either pylorus-preserving or classic PD with either an open or laparoscopic approach. In cases where patients were found to be unresectable in the OR, palliative gastrojejunostomy (GJ) and/or hepaticojejunostomy (HJ) was performed, if indicated. Those who underwent NAC were initiated on a course of FOLFIRINOX with the intention of completing a course of 6 cycles. When patients were not able to tolerate FOLFIRINOX, a regimen of gemcitabine and abraxane was used. Treatment was considered complete when the patient received the intended number of cycles and demonstrated stability or downstaging on imaging and/or a decrease in their CA19-9, and were at that stage recommended for resection. Patients with minimal or no response to NAC on restaging underwent a course of CRT. Active treatment was considered incomplete if the patient was unable to tolerate chemotherapy, or demonstrated progression on restaging imaging and changed course to a palliative regimen.

Outcomes

The primary outcome was median OS and survival at 1 and 3 years. Survival was measured from either the time of initiation of neoadjuvant chemotherapy, or surgical treatment. Secondary outcomes included negative (R0) resection margins, resection rate, time to recurrence, lymph node involvement, length of stay (LOS), and 30-day morbidity (Clavien–Dindo Index). In the group receiving NAC and subsequent operative management, the response to chemotherapy was assessed, and their characteristics were compared to those who did not undergo operative management.

Statistical analysis

Analyses were performed using STATA software (Stata/BE 17.0, StataCorp.). Patients were categorized as either receiving NAC, or undergoing US. Data were analyzed using means with standard deviations, medians with interquartile ranges (IQRs), and frequencies. Comparisons between patient groups

Table 1. Patient demographics comparing the NAC and US groups

	NAC (n = 40)	US (n = 46)	*p*
Age (yr)	65.56 ± 9.31	65.34 ± 9.93	0.92
Sex			0.42
Male	20 (50.0)	19 (41.3)	
Female	20 (50.0)	27 (58.7)	
Comorbidities	5 (4–5.5)	4 (3–5)	0.58
Pre-treatment CA19-9 (μ/mL)	343 (66–890.5)	326 (125–800)	0.58
Pre-treatment total bilirubin (μmol/L)	18.45 (8.05–49.3)	14 (7.4–24)	0.37
Pre-treatment hyperbilirubinemia	19 (47.5)	22 (47.8)	0.98
Adjuvant chemotherapy	13 (46.4)	28 (60.9)	0.17
Vascular involvement			0.11
None	7 (17.5)	12 (26.1)	
SMV-PV	25 (62.5)	15 (32.6)	
SMA	2 (5.0)	3 (6.5)	
CHA	0 (0)	1 (2.2)	
Multivessel	4 (10.0)	7 (15.2)	
Not reported	2 (5.0)	8 (17.4)	

Multivessel: greater than 1 vessel involved. Age presented as mean ± standard deviation. Comorbidities scored according to the Charlson Comorbidity Index.
Comorbidities, pre-treatment CA19-9 and pre-treatment total bilirubin presented as a median and IQR. Hyperbilirubinemia defined as > 21 μmol/L.
NAC, neoadjuvant chemotherapy; US, upfront surgery; CA19-9, carbohydrate antigen 19-9; SMV-PV, superior mesenteric vein or portal vein; SMA, superior mesenteric artery; CHA, common hepatic artery; IQR, interquartile range.

were conducted using Student's t-test, Mann–Whitney U test, and chi-square analysis, as appropriate. Survival analysis was conducted using a Kaplan–Meier curve and log-rank test. Time to death, controlling for our selected covariates, was analyzed using a Cox proportional hazard regression model. Patients were censored if they were lost to follow-up, or did not die prior to the end of the study period. Covariates were selected based on knowledge of known confounders. Given the number of

Table 2. Oncologic and perioperative outcomes

	NAC (n = 40)	US (n = 46)	*p*
Survival			
Median (mon)	19.8 (8.4–44.23)	10.6 (6.37–17.6)	< 0.001[a]
1 yr	28 (70.0)	19 (41.3)	0.008[a]
3 yr	17 (42.5)	5 (10.9)	0.001[a]
Unresectable			
Preoperative	12 (13.95)	N/A	-
At OR	4 (14.3)	17 (37.0)	0.04[a]
Resection rate	24 (60.0)	29 (63.0)	0.77
R0 margins	22 (91.7)	19 (65.5)	0.02[a]
LN metastasis	14 (58.3)	21 (72.4)	0.28
Time to recurrence (day)	276.5 (144.5–359)	266 (94–416)	0.81
LOS (day)	10 (7–13)	11.5 (9–16)	0.09
30-day morbidity	2 (1–3)	2 (1–3)	0.39
Severe complication	5 (17.9)	7 (15.2)	0.74

Median overal survival, time to recurrence LOS and 30-day morbidity (CD) presented as a median and IQR. Severe complication defined as a CD Index score of 3 or higher.
NAC, neoadjuvant chemotherapy; US, upfront surgery; N/A, not available; OR, operative room; R0 margin, negative resection margin; LN, lymph node; LOS, length of stay; CD, Clavien-Dindo Index; IQR, interquartile range.
[a]Denotes significant result.

outcomes (56), we aimed to include 5 covariates in the model, and selected the best-fitting model based on the Akaike Information Criterion. The final model assessed the association between NAC and time to death, adjusting for age, sex, pre-treatment of CA19-9, R0 margin status, and lymph node metastasis. All analyses were conducted as intention-to-treat. A receiver–operator characteristics (ROC) curve was constructed to assess the discriminatory capability of using CA19-9 > 100 μ/mL as a predictor of resectability and mortality.

RESULTS

Study population

Of the 86 patients identified with BRPC, 40 underwent NAC, while 46 underwent US. The two groups had similar distributions of age, sex and comorbidities and pre-treatment of CA19-9; similar median pre-treatment total bilirubin and proportion of patients presenting with hyperbilirubinemia; and a similar distribution of vascular involvement on imaging (Table 1).

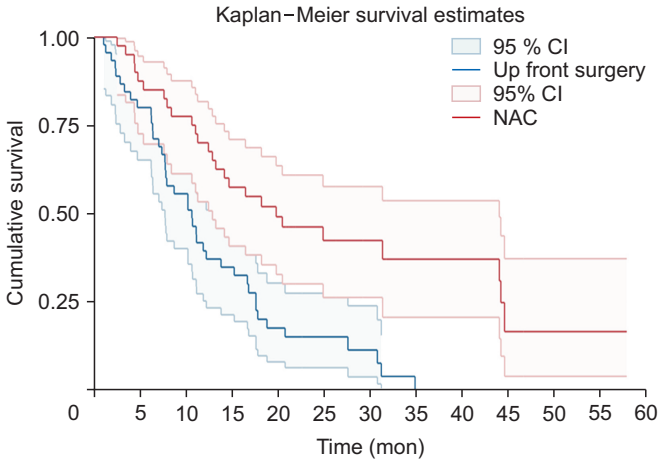

Fig. 1. Kaplan–Meier Survival Curve comparing overall survival (OS) with 95% CIs for NAC compared to upfront surgery. The NAC group showed significantly greater OS (log–rank test *p*-value < 0.001). CI, confidence interval; NAC, neoadjuvant chemotherapy.

Survival

The NAC group showed significantly greater OS than those undergoing US (log-rank $p < 0.001$) (Table 2). Fig. 1 demonstrates the Kaplan–Meier survival function comparing NAC to US. The median OS for the neoadjuvant group was 19.8 months (IQR, 10.3–44.24) vs. 10.6 months (IQR, 6.37–17.6) for those undergoing US (Table 2). At 1 year, 70% (n = 28) of the NAC group were alive, compared to 41.3% (n = 19) of the US group ($p = 0.008$). At 3 years, 42.5% (n = 17) of the NAC group were alive, compared to 10.9% (n = 5) of the US group ($p = 0.001$). Table 3 shows the adjusted and unadjusted analyses using Cox regression. NAC significantly reduced the hazard of death (hazard ratio [HR], 0.20; 95% confidence interval [CI], 0.07–0.54) in comparison to US ($p = 0.001$), when adjusting for age, sex, CA19-9, R1/2 margins, and lymph node metastases. Positive margins and lymph node metastases on pathology were found to increase the hazard of death, though not significantly on adjusted analysis. There were no other independent risk factors for death among these covariates.

To assess CA19-9 as a predictor of mortality, a ROC curve was constructed. The area under the curve (AUC) was 0.6119 (95% CI, 0.4735–0.7501). The cut point of > 100 μ/mL, as pre-determined by our institution as a criterion for borderline resectability, showed 76.79% sensitivity and 29.41% specificity, with a positive predictive value of 1.08 and negative predictive value of 0.789. A CA19-9 level > 500 μ/mL that has been commonly used in previous analyses demonstrated 37.5% sensitivity and 82.35% specificity within our dataset.

Perioperative outcomes

Of the 40 patients undergoing NAC, 30% (n = 12) were ultimately deemed to be unresectable, and did not undergo an

Table 3. Unadjusted and adjusted Cox regression analyses

	Unadjusted			Adjusted		
	HR	95% CI	*p*	HR	95% CI	*p*
NAC	0.39	0.23–0.65	< 0.001[a)]	0.20	0.07–0.54	< 0.001[a)]
CA19-9 (μ/mL)	1.00	1.00–1.00	< 0.001[a)]	1.00	0.99–1.00	0.91
Age	1.01	0.98–1.03	0.64	1.03	0.98–1.08	0.26
Sex	0.97	0.60–1.57	0.92	0.82	0.34–1.99	0.66
R1/2 margins	3.02	1.47–6.24	0.003[a)]	2.23	0.90–5.85	0.08
LN metastases	1.66	0.82–3.41	0.16	1.17	0.48–2.87	0.73

HR, their 95% CIs and Wald test *p*-values are presented. Reference groups are no NAC (upfront surgery), male sex, R0 margins and no LN metastasis. NAC significantly reduced the hazard of death on adjusted analysis.

HR, hazard ratio; NAC, neoadjuvant chemotherapy; CA19-9, carbohydrate antigen 19-9; R1/2 margins, microscopically or macroscopically positive resection margins; LN, lymph node; CI, confidence interval.

[a)]Denotes significant result.

operation (Table 2). Of the patients undergoing operative management, 14.3% and 37.0% (n = 4 and 17) of the NAC and US group, respectively, were found to be unresectable (p = 0.04). Considering all eligible patients, the resection rate in the NAC group and the US group was 60% and 63%, respectively (p = 0.77). The two groups had similar median LOS (10 vs. 11.5 days, p = 0.09), median Clavien–Dindo Index 30-day morbidity (2 vs. 2, p = 0.39), and rate of severe (CDIII or higher) complications (17.9% vs. 15.2%, p = 0.74) (Table 2). Of those who underwent NAC and experienced a severe complication, 2 developed an intra-abdominal abscess requiring drain insertion by interventional radiology (IR), 2 developed delayed gastric emptying (DGE) requiring prolonged nasogastric (NG) tube decompression and total parenteral nutrition (TPN), and 1 patient developed an upper gastrointestinal bleed secondary to vascular angioectasia in the setting of neoadjuvant chemoradiation. Of those who underwent US and experienced a severe complication, 2 developed an intra-abdominal abscess requiring drain insertion by IR, 1 experienced DGE requiring prolonged NG tube decompression and TPN, 1 required re-operation for postoperative bleeding, 1 required re-operation for fascial dehiscence, 1 experienced respiratory distress on postoperative d 3 requiring re-intubation, and 1 patient required multiple re-operations for postoperative bleeding and devel-

Table 4. Subgroup comparison of patients who received NAC, and either went on to operative management, or did not

	Operative (n = 28)	Non-operative (n =12)	p
Age (yr)	65.78 ± 8.5	65.1 ± 11.37	0.82
Sex			> 0.99
Female	14 (50.0)	6 (50.0)	
Male	14 (50.0)	6 (50.0)	
CCI	5 (4–5)	4 (3.5–6)	0.29
Survival			
Median	44.1 (18.2–44.63)	6.1 (4.37–10.63)	< 0.001[a]
1 yr	25 (89.3)	2 (16.7)	< 0.001[a]
3 yr	17 (60.7)	0 (0)	< 0.001[a]
Pre-treatment CA19-9 (μ/mL)	234.5 (47.5–432)	1,127 (251–1,761.5)	0.01[a]
Pre-treatment total bilirubin (μmol/L)	20.65 (8.6–45.35)	11.4 (7.85–56.8)	0.60
Pre-treatment hyperbilirubinemia	14 (50.0)	5 (41.7)	0.63
Vessel involvement			0.02[a]
None	6 (21.4)	1 (8.3)	
SMV-PV	19 (67.9)	6 (50.0)	
SMA	1 (3.6)	1 (8.3)	
Multivessel	0 (0)	4 (33.3)	
Not reported	2 (7.1)	0 (0)	
Criteria for borderline			0.05
Imaging	18 (64.3)	3 (25.0)	
CA19-9	4 (14.3)	2 (16.7)	
Both	6 (21.4)	7 (58.3)	
Chemo completion	26 (92.9)	7 (58.3)	0.008[a]
Number of cycles	5 (4–6)	4.5 (3–6)	0.74
Chemo regimen			0.64
FOLFIRINOX	21 (75.0)	8 (66.7)	
Gem/Abraxane	3 (10.7)	3 (25.0)	
Regimen change	3 (10.7)	1 (8.3)	
5-FU	1 (3.6)	0 (0)	
Neoadjuvant chemoradiation	6 (21.4)	2 (16.7)	0.73

Age is presented as a mean ± standard deviation.
CCI, pre-treatment CA19-9, pre-treatment total bilirubin and no. of chemo cycles are presented as a median and IQR. Comorbidities scored according to the Hyperbilirubinemia defined as > 21 μmol/L.
NAC, neoadjuvant chemotherapy; CA19-9, carbohydrate antigen 19-9; SMV-PV, superior mesenteric vein or portal vein; SMA, superior mesenteric artery; CCI, Charlson Comorbidity Index; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; Gem/Abraxane, Gemcitabine/Abraxane; Regimen change, patients who were initiated on FOLFIRINOX then switched to Gemcitabine/Abraxane due to poor tolerance; 5-FU, 5-fluorouracil.
[a]Denotes significant result.

oped a hepatic artery to jejunal fistula and multiple enteric leaks, ultimately resulting in death.

Oncologic outcomes

Of the patients who underwent resection, those who received NAC had a significantly greater R0 resection rate (91.7% vs. 65.5%, $p = 0.02$), and a lower but not statistically significant rate of lymph node metastases (58.3% vs. 72.4%, $p = 0.28$). The two groups had comparable median time to recurrence (276.5 days vs. 266 days, $p = 0.81$) (Table 2).

Neoadjuvant chemotherapy: operative vs. non-operative patients

Of the patients undergoing NAC, 70% (n = 28) underwent operative management, while 30% (n = 12) were ultimately deemed to be unresectable after NAC (Table 4). These two subsets of patients displayed a similar distribution of age, sex, and pre-operative comorbidities. The non-operative group had a significantly higher pre-treatment CA19-9 (1,127 vs. 234.5, $p = 0.01$). Both groups had similar median total bilirubin and proportion of patients with hyperbilirubinemia. In terms of criteria for being borderline resectable, the operative group had a higher rate of being diagnosed on imaging of 64.3% vs. 25% and a lower rate of being diagnosed by both imaging and CA19-9 level of 21.4% vs. 58.3%, in comparison to those who were non-operative ($p = 0.024$). The operative group had a greater proportion of patients with no vascular involvement of 21.4% vs. 8.3% and lower proportion of patients with multivessel involvement of 0% vs. 33.3%, in comparison to the non-operative group. Between the subgroups, there was no significant difference in the number of chemotherapy cycles, the chemotherapeutic regimen, or the rate of addition of neoadjuvant radiation. The operative group had a higher chemotherapy completion rate than the non-operative group (92.9% vs. 58.3%, $p = 0.008$). In the operative group, 45% (n = 9) of CA19-9 secretors (n = 20) showed a decrease in their CA19-9 post-NAC, 67.9% (n = 19) had a decrease in tumor size on re-staging imaging, and 54.2% (n = 13) of patients who underwent curative resection showed at least a partial pathologic response in their tumor specimen. Forty-five percent (n = 9) had an increase in their CA19-9 post-treatment. Ten of the non-operative patients had their CA19-9 re-assessed during neoadjuvant treatment. Of the 9 who were CA19-9 secretors, only 2 showed a decrease in their level, whereas 7 showed an increase. Nine of the non-operative patients experienced disease progression while on NAC, while the remaining 3 showed no response (Table 4).

A ROC curve was constructed to analyze CA19-9 as a predictor of unresectability among patients who received NAC. The AUC was 0.7083 (95% CI, 0.54–0.88). A CA19-9 level > 100 μ/mL had 75% sensitivity and 33.3% specificity with an LR+ of 1.13 and LR– of 0.75.

FOLFIRINOX vs. other regimens

Twenty-nine patients (72.5%) received FOLFIRINOX, 6 (15.0%) received Gemcitabine/abraxane, 4 (10.0%) were initiated on FOLFIRINOX, then switched to Gemcitabine/abraxane due to chemotherapy intolerance, and 1 (2.5%) received only 5-fluorouracil (5-FU). Those who received FOLFIRINOX underwent a median of 5 cycles of chemotherapy (IQR, 4–6), while those who received any of the other regimens underwent a median of 3.5 cycles (IQR, 3–6). There was no significant difference in the rate of R0 margin status (89% with FOLFIRINOX vs. 100% with other regimens, $p = 0.45$) or lymph node positivity status (42.1% with FOLFIRINOX vs. 40% with other regimens, $p = 0.93$) between chemotherapeutic regimens among those who eventually underwent resection. The median OS was 18.2 months (IQR, 8.3–25.3 months) for those receiving FOLFIRINOX, and 14.7 months (IQR, 11–26.3 months) for those receiving another regimen. There was no significant difference in 1 or 3 year survival between these two groups. At 1 year, 19 (65.5%) patients who received FOLFIRINOX were alive, while 8 (72.7%) who received another regimen were alive ($p = 0.63$). At 3 years, 13 (44.8%) patients who received FOLFIRINOX were alive, while 4 (36.4%) who received another regimen were alive ($p = 0.63$).

DISCUSSION

This study presents the experience of a single institution utilizing neoadjuvant FOLFIRINOX for BRPC, as defined by either tumor anatomy or biology, since this regimen became first-line treatment at our institution for this patient population in 2018. Although neoadjuvant therapy has demonstrated remarkable benefit for patients with BRPC, an optimal regimen has yet to be defined. Based on the intention to treat analysis, NAC demonstrated an OS benefit in addition to improved survival at 1 and 3 years, in comparison to US. Our study demonstrated a median OS of 19.8 months in all patients undergoing NAC. In patients who were considered for curative resection, median OS was 44.1 months, which is elevated compared to previous studies of BRPC, and greater than reports of patients with resectable tumors who underwent NAC [16]. Meta-analysis of patients undergoing various regimens of NAT for BRPC have demonstrated median OS ranging 17.9–20 m and improving to 25.9–30 m if resected, a resection rate of 62%–85.3%, laparotomy rate of 65.3%–71%, and R0 margins in 57.4%–97% of patients [4,16-18]. A patient-level meta-analysis of studies that used FOLFIRINOX as first-line treatment found a pooled resection rate of 67.8%, pooled R0 resection rate of 83.9% and pooled median OS of 22.2 m [9]. Two recent phase 2 clinical trials have supported the use of FOLFIRINOX along with CRT for BRPC, owing to a favorable R0 resection rate of 100% and 97%, respectively, of individuals undergoing curative resection [19,20]. While the primary outcome of both these studies was R0 resection, they also reported favorable median

progression-free survival and median OS [19,20].

Similar to what has been described in the literature, we found a 60% resection rate and a 76.6% R0 resection rate when curative resection was undertaken. The NAC group resection rate was similar to that of patients undergoing US; however, only 4 (14.3%) of the patients undergoing NAC and taken to the OR were found to be unresectable at laparotomy, whereas 12 (13.95%) were identified pre-operatively to have progressed while on NAC, and were spared the morbidity of a laparotomy and potential resection that would not have benefitted them.

This study identified the use of NAC as the only independent predictor of improved survival among the covariates analyzed with Cox regression. Previous studies have identified additional predictors of survival including baseline CA19-9, change in CA19-9, R0 margins, tumor size, comorbidities, pathological response, and extended chemotherapy [13,21]. CA19-9 has been described in numerous studies as a valuable prognostic indicator, and while evidence suggests that higher pre-treatment of CA19-9 is associated with reduced resection rate and worse survival in both anatomically BRPC and anatomically resectable PDAC patients, there is no consensus regarding a clinically relevant cut-off point for predicting resection and survival [22-29]. The International Association of Pancreatology (IAP) defines biologically borderline resectable as a CA19-9 value > 500 μ/mL, which has been assessed in other studies [10,22,30]. However, multiple other cut-off points ranging 120–1,000 μ/mL have also been associated with poor resection rate and worse OS [27,28,31]. Others have described the change in CA19-9 from pre- to post-therapy as a stronger prognosticator than baseline CA19-9 [24,32].

Using our institution's unique definition of biologically BRPC as CA19-9 > 100 μ/mL regardless of anatomical involvement, we did not find CA19-9 to be an independent predictor of survival on multivariate analysis, and it showed poor discrimination in predicting mortality. This may be partly due to selecting a patient population with abnormally elevated CA19-9 by definition and high mortality rate. Within the NAC group, those who were eventually recommended for surgery had a significantly lower pre-treatment of CA19-9 than those who were eventually deemed to be non-operative. Nearly all of those who did not go on to operative management experienced an increase in post-treatment of CA19-9. In the NAC subset, CA19-9 was a moderate predictor of resection. Our cut-off of CA19-9 > 100 μ/mL yielded 76.79% sensitivity and 29.4% specificity as a predictor of death, and 75% sensitivity and 33.3% specificity as a predictor of resection. Given the heterogeneity in the current literature, future work is necessary to define a consensus on the optimal cut-off for CA19-9 as a prognostic factor for survival and resection.

The prospective aspect of this study allowed us to identify all patients undergoing NAC from 2018 onward and characterize those who when on to surgery, and importantly, those who did not. While the non-operative subset represents a small sample, they appear to have more aggressive disease at baseline, owing to their elevated pre-treatment of CA19-9, greater proportion of multivessel involvement, and lower rate of chemotherapy completion than the operative subgroup. Furthermore, most of this group experienced an increase in CA19-9 post-NAC, and evidence of disease progression on re-staging. While some studies have identified elevated CA19-9 as a predictor of unresectable disease, others have not identified any significant predictors of resection for BRPC, although concluding that lower CA19-9 and smaller tumor size are favorable characteristics [27,31,33,34].

The major limitation of this study is that this is a retrospective review of an institutional database that was both retrospectively populated and prospectively maintained. This characteristic of the available data inherently limits the hypotheses that can be addressed, such as limiting the analysis of postoperative complications to within a 30 d period. While this study demonstrates the safety and efficacy of NAC with FOLFIRINOX for BRPC at our institution, we present a single institution's experience that may not be generalizable to dissimilar patient populations.

In conclusion, we found a survival benefit of NAC with FOLFIRINOX for BRPC, compared with US. The R0 margin rate and lymph node metastasis also improved, though not significantly. Greater pre-treatment of CA19-9 and multivessel involvement on initial staging imaging were associated with progression of disease following NAC and no eventual operative management. Although further work is needed to determine the optimal CA19-9 cut-off value for prognosticating survival and resectability, this study supports the utility of NAC in pre-operatively selecting out-patients who are at high risk of progression despite treatment, and would thus be unlikely to benefit from surgical management, while improving survival in those who undergo surgical resection.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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