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Survival of patients with borderline resectable pancreatic cancer who received neoadjuvant therapy and surgery

Chad A. Barnes[a], Mariana I. Chavez[a], Susan Tsai[a], Mohammed Aldakkak[a], Ben George[b], Paul S. Ritch[b], Kulwinder Dua[c], Callisia N. Clarke[a], Parag Tolat[d], Catherine Hagen[e], William A. Hall[f], Beth A. Erickson[f], Douglas B. Evans[a], Kathleen K. Christians, MD[a,*]

[a] Pancreatic Cancer Program, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI
[b] Pancreatic Cancer Program, Department of Medicine, Division of Hematology Oncology, Medical College of Wisconsin, Milwaukee, WI
[c] Pancreatic Cancer Program, Department of Medicine, Division of Gastroenterology, Medical College of Wisconsin, Milwaukee, WI
[d] Pancreatic Cancer Program, Department of Radiology, Medical College of Wisconsin, Milwaukee, WI
[e] Pancreatic Cancer Program, Department of Pathology, Medical College of Wisconsin, Milwaukee, WI
[f] Pancreatic Cancer Program, Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI

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ABSTRACT

Background: It is difficult to successfully deliver multimodality therapy to patients with operable pancreatic cancer. Data on the natural history of such efforts are necessary for physicians to guide shared decision-making with patients and families. We report the survival of consecutive patients with borderline resectable pancreatic cancer who received neoadjuvant therapy before surgery.

Methods: Data regarding demographics, neoadjuvant therapy, surgery, pathology, and survival duration were abstracted on consecutive patients with borderline resectable pancreatic cancer diagnosed between 2009 and 2017 and not treated on available clinical trials. Borderline resectable pancreatic cancer was defined based on ≥1 of the following: local tumor anatomy, pretreatment serum carbohydrate antigen 19-9 >2,000 U/mL, and the presence of radiographic lesions indeterminate for metastases.

Results: Neoadjuvant therapy was delivered to 185 patients with borderline resectable pancreatic cancer who were not enrolled in competing clinical trials; 13 (7%) patients received chemoradiation, 12 (7%) received chemotherapy, and 160 (86%) received both. Of the 185 patients, 115 (62%) completed all intended neoadjuvant therapy and surgery; 81 (70%) of 115 underwent pancreaticoduodenectomy; and vascular reconstruction was performed in 51 (44%). A margin negative resection was achieved in 111 (97%) of 115 patients, and 83 (72%) were node negative. Median overall survival for all 185 patients was 20 months; 31 months for the 115 patients who completed all neoadjuvant therapy and surgery as compared to 13 months for the 70 patients who were not resected ($P < .0001$).

Conclusion: After neoadjuvant therapy, surgical resection was performed in 62% of patients with borderline resectable pancreatic cancer. Those who normalized preoperative serum carbohydrate antigen 19-9 and had node negative pathology achieved the longest survival. To further improve median survival for all patients, we are incorporating adaptive approaches to neoadjuvant therapy sequencing based on objective assessments of response.

Introduction

Borderline resectable (BLR) is a clinical stage of pancreatic cancer (PC) that carries significant prognostic implications for both patients and treating physicians. Although BLR PC has been defined in various ways, this particular stage, by definition, identifies patients with more advanced local disease.[1–6] Tumors that encase the portal (PV) or superior mesenteric vein (SMV) or abut major arteries, such as the celiac (CA), superior mesenteric (SMA), or common hepatic (CHA), require more technically complex operations. In addition, patients

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* Reprint requests: Kathleen K. Christians, MD, Medical College of Wisconsin, Department of Surgery, 8701 Watertown Plank Rd, Milwaukee, WI, 53226.
E-mail address: kchristi@mcw.edu (K.K. Christians).

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with BLR PC are at higher risk for having micro-metastatic disease at the time of diagnosis.[7,8] As a result, several practice guidelines have advocated for neoadjuvant therapy (NeoTx) before surgical resection for all patients with BLR PC and results from recent prospective clinical trials support these recommendations.[9–13] Data from single or multi-institution prospective trials have the benefit of strict eligibility criteria and data monitoring. They are, however, prone to selection bias and can often include patients with a superior performance status or less advanced disease. Retrospective reviews of consecutive patients at high volume institutions are less prone to selection bias and do provide a real world experience, the results of which are often complimentary to those of prospective clinical trials. For example, we have previously reported the results of NeoTx and surgery in patients with resectable pancreatic cancer; median overall survival (OS) was 44.9 months.[14] The objective of the present study was to report the survival of consecutive patients with BLR PC treated with NeoTx followed by surgery to determine if the favorable results in resectable disease could be replicated in this more advanced stage of disease.

Methods

Study subjects

Using a prospectively maintained PC database, we reviewed consecutive patients who received NeoTx for BLR PC and were not enrolled in an institutional clinical trial and have not been previously reported. This retrospective analysis was approved by the Institutional Review Board of the Medical College of Wisconsin. All patients had histologically confirmed pancreatic ductal adenocarcinoma. Clinical stage at the time of diagnosis was determined using objective radiographic criteria based on computed tomography (CT) imaging, as previously described.[15] BLR PC was anatomically defined as: (1) tumor abutment ($\leq$180 degrees) of the SMA; (2) tumor abutment of the CA; (3) short-segment tumor abutment or encasement (>180 degrees) of the CHA without extension to the CA or CHA bifurcation; or (4) >50% narrowing of the SMV, PV, SMV and PV, or short-segment venous occlusion with suitable proximal and distal targets for reconstruction. In addition, patients were classified as BLR due to the following: (1) the presence of radiographic lesion(s) in the liver or lung judged indeterminate for metastatic disease by radiologists specializing in abdominal imaging; or (2) serum carbohydrate antigen 19-9 (CA19-9) levels >2,000 U/mL. The electronic medical record was reviewed for explicit documentation of comorbid conditions at the time of initial evaluation at our institution, and an age-adjusted Charlson comorbidity index was calculated for each patient.[16]

Neoadjuvant therapy and surgery

Patients who participated in investigator-initiated or cooperative group clinical trials were excluded from the present analysis. The standard treatment algorithm for patients with BLR PC consisted of a minimum of 2 months of induction chemotherapy followed by chemoradiation. The majority of patients received systemic therapy with either 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX), or gemcitabine with nab-paclitaxel. Chemoradiation, when given at our institution, was administered with concurrent gemcitabine (300–400 mg/m^2 at fixed dose rate, infused weekly $\times$ 6) or capecitabine (825 mg/m^2 orally twice daily during the radiation therapy). External-beam radiation therapy was delivered 5 days per week over 5.5 weeks using 3-dimensional conformal or intensity modulated radiation therapy techniques. Patients received a total dose of 50.4 Gy prescribed to the 95% isodose at 1.8 Gy/fraction, Monday to Friday, for a total of 28 fractions. Staging with CT imaging and laboratory studies, including CA19-9, was performed at diagnosis (pretreatment), between chemotherapy and chemoradiation, after completion of all intended NeoTx (preoperative), and after surgery (posttreatment). Serum CA19-9 levels were categorized as normal ($\leq$35 U/mL) or elevated (>35 U/mL). CA19-9 levels measured in the setting of hyperbilirubinemia (>2 mg/dL) were considered not evaluable.

Preoperative restaging occurred approximately 4 weeks after the last radiation fraction. Patients were offered surgery in the absence of disease progression or inadequate performance status. At the time of operation, laparoscopy was routinely performed immediately before laparotomy to evaluate for radiographically occult extrapancreatic disease. Operations including pancreaticoduodenectomy (PD), distal pancreatectomy, or total pancreatectomy were performed as extensively described in prior publications.[17–19] The College of American Pathologists reporting format was utilized for surgical specimens, which was based on the eighth edition of the American Joint Committee on Cancer. The SMA, pancreatic, and hepatic duct margins were considered positive if tumor was present at the margin. Postoperative complications were graded using the Clavien-Dindo classification.[20] Operative mortality was defined as death during the same hospitalization or within 90 days of surgery.

Surveillance

Patients who completed all intended NeoTx and surgery were followed at 4- to 6-month intervals with physical examination, laboratory studies, and CT imaging. In the event of recurrent PC, the date and location of recurrence and treatment were recorded. Disease recurrence was assessed radiographically and confirmed with tissue biopsy only when the radiographic abnormality was atypical or if molecular profiling of recurrent tumor tissue was requested. Sites of first failure were classified as local for recurrences in the pancreas, resection bed or along the peripancreatic vasculature, regional for recurrences in the peritoneum, retroperitoneum, or abdominal wall, and distant for recurrence at all other organ sites.

Statistical analysis

Categorical variables were compared using the Fisher exact or χ^2 test. All continuous variables were analyzed using the Mann-Whitney *U* test. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease recurrence. Overall survival (OS) and follow-up were calculated from the date of diagnosis to the date of death or last follow-up. Deaths from any cause were included in the survival analysis. OS was estimated using the method of Kaplan and Meier. We tested proportional hazard assumptions for all variables associated with survival. Clinical factors were included in the multivariable model if the univariable had a $P < .20$. All statistical analyses were performed using Stata 14.2 (StataCorp, College Station, TX).

Results

Between 2009 and 2017, 262 consecutive patients with BLR PC were evaluated at Medical College of Wisconsin; 69 (26%) were enrolled in a prospective clinical trial and 8 (3%) were thought not to be candidates for surgery owing to poor performance status or significant comorbid conditions. Of the remaining 185 patients, 90 (49%) were female, the median age was 65 years (interquartile range [IQR] 12 years), and the median Charlson comorbidity index was 5 (IQR 2). Demographic data are summarized in Table I. Before referral, 13 (7%) were taken to surgery but not resected owing to vascular involvement

Table I
Demographic data for all patients

Variables	Total n = 185	Resected n = 115	Not resected n = 70	*P* value
Sex, *n* (%)				.99
Female	90 (49)	56 (49)	34 (49)	
Male	95 (51)	59 (51)	36 (51)	
Age, median (IQR)	65 (12)	64 (11)	65 (15)	.60
Body mass index, median (IQR)	26.5 (7.5)	26.8 (7.5)	26.2 (6.5)	1.00
Charlson Comorbidity Index, median (IQR)	5 (2)	5 (2)	5 (2)	.01
CA19-9 at diagnosis, median (IQR)*	385 (893)	350 (789)	460 (1149)	.63
Neoadjuvant therapy, *n* (%)				<.001
Chemotherapy	12 (7)	0 (0)	12 (17)	
Chemoradiation	13 (7)	4 (3)	9 (13)	
Both	160 (86)	111 (97)	49 (70)	
Preoperative CA19-9, *n* (%)				<.001
≤35 U/mL	85 (46)	68 (59)	17 (24)	
>35 U/mL	93 (50)	47 (41)	46 (66)	
Unknown	7 (4)	0 (0)	7 (10)	

* Median value for only patients who were elevated at diagnosis (CA19-9 >35 U/mL).

or metastatic regional lymph nodes; 11 (6%) of these patients underwent bypass operations and 2 (1%) underwent exploration only.

Neoadjuvant therapy

Of the 185 patients, 69 (37%) had begun or completed NeoTx at the referring facility before consultation at our institution and 116 (63%) began NeoTx under the direction of our multidisciplinary team. Of the 69 patients who were treated before referral, 40 (58%) had received chemotherapy, 5 (7%) had received chemoradiation, and 24 (35%) had received both chemotherapy and chemoradiation. Of the 40 patients who received neoadjuvant chemotherapy before referral, 16 (40%) completed chemoradiation at our institution. Of the 116 patients who were evaluated at our institution before receiving treatment, 24 (21%) received chemotherapy at an outside facility and received chemoradiation at our institution, 32 (27%) received all NeoTx at an outside facility, and 60 (52%) received all NeoTx at our institution. These later 60 patients were not treated on a clinical trial owing to ineligibility, patient preference, or a short gap between available trials for BLR PC. Overall, 53 (29%) of the 185 patients completed all NeoTx at the referring facility, 60 (32%) received all NeoTx at our institution, and 72 (39%) received NeoTx in a collaborative fashion both at our center and closer to home.

Among the 185 patients, NeoTx consisted of systemic chemotherapy alone in 12 (7%), chemoradiation alone in 13 (7%), and both chemotherapy and chemoradiation in 160 (86%) patients. In total, 172 (93%) of the 185 patients received systemic chemotherapy before surgery and the most common regimens utilized were FOLFIRINOX, which was given to 89 (51%) patients and gemcitabine with nab-paclitaxel, which was administered to 31 (18%) patients (Table II). In total, 173 (93%) of the 185 patients received preoperative radiation therapy, which consisted of gemcitabine-based chemoradiation in 121 (70%), capecitabine-based chemoradiation in 49 (28%), and bevacizumab- and erlotinib-based chemoradiation in 1 (1%). Conventional fractionation (1.8 Gy/fx) was used in 171 of the 173 patients; one patient received hypofractionated radiation, and one patient received stereotactic body radiation therapy.

Pretreatment and posttreatment (preoperative) CA19-9

At diagnosis, 141 (76%) of the 185 patients had an evaluable pretreatment serum CA19-9 value. Of these 141 patients, 40 (28%) had a normal pretreatment CA19-9 (nonproducers) and 101 (72%) had an elevated CA19-9. The median CA19-9 level in these 101 patients was 385 U/mL (IQR 893 U/mL), and 13 (13%) had a CA19-9 >2,000 U/mL. After NeoTx, 97 (95%) of the 101 patients with an elevated pretreatment value had an evaluable preoperative CA19-9. Of these 97 patients, 38 (39%) normalized their CA19-9 after NeoTx and 59 (61%) did not. Of the 59 patients who failed to normalize their preoperative CA19-9, 28 (47%) underwent successful surgery; 10 (36%) of these 28 patients normalized their postoperative CA19-9.

Table II
Types of neoadjuvant therapy (all patients)

	Total
Chemotherapy	172
FOLFIRINOX, *n* (%)	75 (43)
FOLFIRINOX plus 5-Fluorouracil or Gemcitabine-based therapy, *n* (%)	14 (8)
FOLFOX plus Gemcitabine-based therapy, *n* (%)	2 (1)
Other 5- Fluorouracil-based therapy, *n* (%)	3 (2)
Gemcitabine/Nab-paclitaxel, *n* (%)	31 (18)
Gemcitabine/Cisplatin, *n* (%)	25 (15)
Gemcitabine monotherapy, *n* (%)	13 (8)
Other Gemcitabine-based therapy, *n* (%)	9 (5)
Chemoradiation	173
Gemcitabine-based, *n* (%)	121 (70)
Capecitabine-based, *n* (%)	49 (28)
Other radiation therapy, *n* (%)	3 (2)

Surgical and pathologic outcomes

Of the 185 patients, 51 (28%) were thought not to be candidates for surgery at the time of preoperative restaging owing to disease progression ($n = 26$, 14%), inadequate performance status ($n = 18$, 10%), or both ($n = 7$, 4%). Of the 33 patients who evidenced disease progression during or after NeoTx, 15 (45%) had radiographic lesions indeterminate for metastatic disease at diagnosis. Surgery was offered to 134 (73%) of the 185 patients; however, 2 patients declined. Of the 132 (71%) patients who proceeded to surgery, 17 (13%) were found to have radiographically occult metastases at the time of laparoscopy and were not resected. Of these 17 patients with occult metastases, 4 (24%) had a CA19-9 >2,000 U/mL at diagnosis and 7 (41%) had radiographic lesions indeterminate for metastatic disease at diagnosis. In total, 115 (62%) of the 185 patients completed all intended NeoTx and surgery (Fig 1). The majority of operated patients underwent standard PD ($n = 81$, 70%) and the remaining 34 (30%) patients underwent either pylorus-preserving PD ($n = 3$, 3%), distal pancreatectomy ($n = 16$, 14%), or total pancreatectomy ($n = 15$, 13%). Vascular resection with reconstruction was required in 51 (44%) of the 115 patients; 44

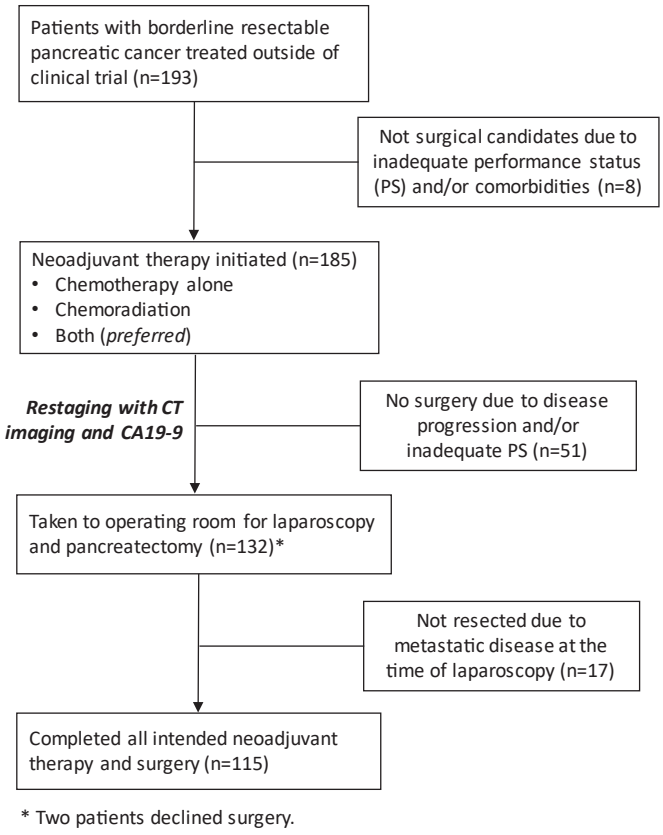

Fig 1. Flow diagram for patients with borderline resectable pancreatic cancer evaluated at our institution.

(38%) underwent venous resection and reconstruction alone, 1 (1%) underwent arterial resection and reconstruction alone, and 6 (5%) patients underwent both venous and arterial resection and reconstruction. Of the 51 patients who required vascular resection(s), temporary mesocaval shunting was performed in 5 (10%) to facilitate a safe portal dissection in the setting of cavernous transformation of the PV. Creation of a distal splenorenal bypass was performed in 11 (22%) patients who required splenic vein (SV) ligation and had an inferior mesenteric vein, which entered directly into the SMV and therefore did not decompress the SV.

Pathologic outcomes are summarized in Table III. Overall, margin negative (R0) resections were achieved in 111 (97%) of the 115 patients. The hepatic duct margin was negative in all 99 patients who underwent either PD or total pancreatectomy. The pancreatic transection margin was positive in 2 (2%) of the 100 patients who underwent either right or left pancreatectomy. In both of these patients the pancreatic transection margin was reported as negative on frozen section evaluation at the time of operation and positive on permanent section histologic evaluation. The SMA margin was positive (tumor at the inked margin) in 2 (2%) of the 99 patients who underwent either PD or total pancreatectomy. Of the remaining 97 patients who underwent either PD or total pancreatectomy, the SMA margin was negative and <1 mm in 3 (3%) patients, >1 mm in 50 (52%) patients, and negative without distance reported in 44 (45%) patients. The median OS for patients with a negative margin distance <1 mm, margin distance >1 mm, and margin distance unreported were 27 months, 37 months, and 35 months, respectively ($P = .38$). A complete pathologic response (T0) after NeoTx occurred in 8 (7%) of the 115 patients. Node negative disease was found in 83 (72%) of the 115 patients. The median hospital stay after surgery was 8 days (IQR 4 days).

Table III
Clinicopathologic data of resected patients

Variables	Patient(s) n = 115
Operation, *n* (%)	
Pylorus preserving PD*	3 (3)
Standard PD	81 (70)
Distal pancreatectomy	16 (14)
Total pancreatectomy	15 (13)
Vascular resection, *n* (%)	
Arterial resection	1 (1)
Venous resection	44 (38)
Both	6 (5)
Not performed	64 (56)
Venous shunt, *n* (%)	
Mesocaval	4 (3)
Splenorenal	10 (9)
Both	1 (1)
Not performed	100 (87)
Duration of hospital stay, median (IQR)	8 (4)
Margin, *n* (%)	
Negative	111 (97)
Positive	4 (3)
T stage, *n* (%)	
T0	8 (7)
T1	28 (24)
T2	55 (48)
T3	24 (21)
N stage, *n* (%)	
N0	83 (72)
N1	27 (24)
N2	5 (4)
Perineural invasion, *n* (%)	
No	50 (43)
Yes	64 (56)
Unknown	1 (1)
Lymphovascular invasion, *n* (%)	
No	90 (78)
Yes	21 (18)
Indeterminate	4 (4)
Postoperative CA19-9, *n* (%)	
≤35 U/mL	79 (69)
>35 U/mL	31 (27)
Unknown	5 (4)
Postoperative complications	
Pancreatic fistula	3 (3)
Postoperative hemorrhage	2 (2)
Death	2 (2)

Postoperative complications occurred in 62 (54%) of the 115 patients who underwent surgery; 44 (38%) had either Clavien-Dindo grade 1 or 2 complications, 14 (12%) had grade 3 complications, 2 (2%) had grade 4 complications, and 2 (2%) had grade 5 complications. Of the 2 patients with grade 4 complications, the first experienced a postoperative hemorrhage after standard PD with SMV/PV resection and distal splenorenal bypass. This patient was taken back to the operating room for relaparotomy; however, the source was not identified and there was no active blood loss at the time of reoperation. The patient had an otherwise uncomplicated hospital course and was discharged to home on postoperative day 8. The second patient with a grade 4 complication developed a postoperative pancreatic fistula-associated sepsis and multisystem organ dysfunction. The fluid collection was managed with intravenous antibiotics and image-guided percutaneous drainage. After a prolonged hospital course, the patient was discharged to home. Of the 2 patients who experienced grade 5 complications, the first had an unexpected, fatal cardiac event in the recovery room after an uneventful operation. The second patient developed decompensated hepatic failure postoperatively (not appreciated preoperatively in the setting of normal liver perfusion), which required multiple paracenteses and ultimately a transjugular

Table IV
Clavien-Dindo grades 3, 4, and 5 complications

Patients	Age	Operation	Complication grade	Specific complication	Intervention
1	54 y	Standard PD	3	Intra-abdominal fluid collection	Image-guided drain placement
2	58 y	Standard PD	3	Bacteremia	Mediport removal
3	59 y	Standard PD	3	Intra-abdominal fluid collection	Image-guided drain placement
4	59 y	Standard PD	3	Ascites	Paracentesis
5	69 y	Standard PD	3	Ascites	Paracentesis
6	65 y	TP	3	Gastrointestinal bleed of unclear cause	Upper and lower endoscopy
7	72 y	DP	3	Pancreatic fistula	Image-guided drain placement
8	57 y	Standard PD	3	Chylous ascites	Paracentesis
9	81 y	Standard PD	3	Gastroduodenal artery aneurysm	Coil embolization
10	65 y	DP	3	Pancreatic fistula	Image-guided drain placement
11	64 y	TP	3	Ascites	Paracentesis
12	66 y	Standard PD	3	Enterocutaneous fistula at jejunostomy tube site	Resection of fistula track
13	68 y	Standard PD	3	Gastric outlet obstruction secondary to edema at GJ anastomosis	Upper endoscopy with balloon dilation of GJ anastomosis
14	72 y	Standard PD	3	Retroperitoneal lymphocele	Image-guided drain placement
15	70 y	Standard PD	4	Postoperative hemorrhage	Relaparotomy with evacuation of hematoma
16	61 y	DP	4	Pancreatic fistula with sepsis and multisystem organ dysfunction	Image-guided drain placement
17	55 y	Standard PD	5	Decompensated hepatic failure	Serial paracenteses and transjugular intrahepatic portosystemic shunt
18	77 y	Standard PD	5	Cardiac arrest	Cardiac catherization

DP, distal pancreatectomy; *GJ*, gastrojejunostomy; *PD*, pancreaticoduodenectomy; *TP*, total pancreatectomy.

intrahepatic portosystemic shunt. After a prolonged hospital course, the patient was discharged to a hospice facility and died 37 days from the date of surgery. These 2 (2%) patients represent the only 90-day mortalities among the 115 patients who completed all NeoTx and surgery. Postoperative complications are further described in Table IV.

Survival analysis

The median OS of the 185 patients was 20 months and 31 months for the 115 patients who completed all intended NeoTx and surgery, compared with 13 months for the 70 patients who were not resected (log-rank $P < .0001$; Fig 2). The median follow-up of the 115 resected patients was 26 months and the minimum follow-up for all living patients was 14 months. Of the 115 patients, the median OS of the 68 patients with a normal preoperative CA19-9 was 46 months as compared with 25 months for the 47 patients who had an elevated preoperative CA19-9 after NeoTx (log-rank $P = .0003$; Fig 3). Of all 115 resected patients, the median OS of the 83 patients with node negative disease was 40 months compared with 26 months for the 27 patients with N1 disease and 16 months for the 5 patients with N2 disease (log-rank $P = .0003$; Fig 4).

Of the 115 patients, the median OS of the 50 patients who required venous resection or reconstruction was 27 months as compared with 44 months for the 64 patients who did not undergo any form of vascular resection (log-rank $P = .01$). However, venous resection or reconstruction was not a significant clinical factor associated with survival in an adjusted hazards analysis. There was no difference in median OS among the 7 patients who required arterial resection and reconstruction (with or without vein resection) as compared with the 64 patients who did not undergo any vascular resection (37 months vs 44 months, respectively; log-rank $P = .27$).

In a multivariable cox proportional hazards analysis (including only resected patients), male sex (hazard ratio [HR] 1.82; 95% confidence interval [CI] 1.13–2.94; $P = .01$), elevation of preoperative CA19-9 (HR 1.86; 95% CI 1.16–2.99; $P = .01$), N1 disease (HR 1.69; 95% CI 1.00–2.88; $P = .05$) and N2 disease (HR 4.79; 95% CI 1.75–13.11; $P = .002$) were clinical factors associated with an increased risk of death. The venous resection and reconstruction, pathologic T stage, and perineural invasion were not significant clinical factors associated with survival (Table V).

At the time of this analysis, 69 (60%) of the 115 patients who completed all intended NeoTx and surgery had developed recurrent PC, 37 (32%) were disease free, and 9 (8%) had unknown disease status. For the 106 resected patients with known disease status, the median PFS was 19 months and the site of first recurrence was local-only in 9 (8%), regional-only in 7 (7%), distant-only in 34 (32%), and multisite in 19 (18%) patients. The median PFS for patients with local, regional, distant, and multisite recurrences were 27, 13, 15, and 13 months, respectively (log-rank; $P = .29$).

Discussion

BLR PC was first defined in 2006 by Varadhachary et al to include tumors with short segment SMV-PV occlusion and abutment of the celiac, CHA or SMA, suggesting that borderline tumors, while operable, were likely to require a more complex operation than patients with resectable disease who did not have such vessel involvement.[1] National and international groups have since tried to refine this definition leading to the most recent 2017 update from the NCCN.[2–6,9] There is now general consensus that the definition of BLR PC should include both anatomic (tumor-vessel relationships) and oncologic factors (radiographic findings indeterminate for metastases, positive local-regional lymph nodes or elevated CA19-9 levels beyond a certain threshold) and perhaps patient-related comorbidities and performance status.[18,19] Consensus has also been achieved for NeoTx sequencing to more carefully select those patients with BLR PC likely to benefit from a larger operation of increased risk, thereby avoiding surgery in those patients with disease progression during or after NeoTx. These later patients, if taken directly to surgery, were the ones most likely to experience early disease recurrence.

Beyond treatment sequencing, more recent studies have focused on 2 additional challenges: (1) whether anatomic downstaging can occur or be facilitated by NeoTx and thereby result in a less extensive operation; and (2) the examination of oncologic factors to help determine who should/should not be considered for surgery.[7] To this end, a meta-analysis of FOLFIRINOX compared with gemcitabine-based neoadjuvant regimens found a slightly higher rate of

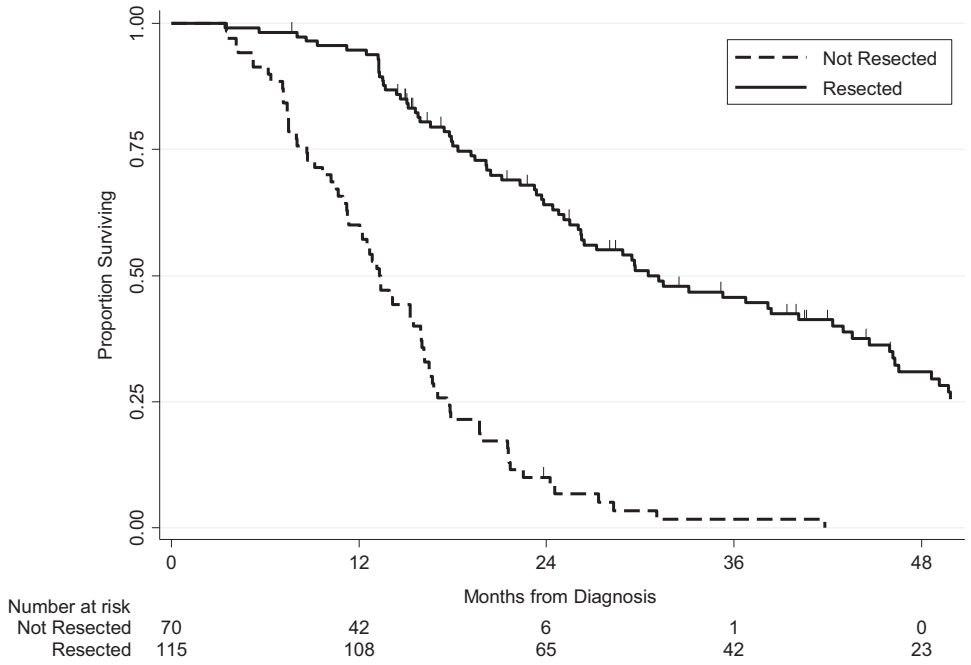

Fig 2. Kaplan-Meier estimates of overall survival by completion of intended neoadjuvant therapy and surgery for all patients. The median overall survival of resected patients (*solid line*) was 31 months as compared to 13 months for unresected patients (*dashed line* $P < .0001$).

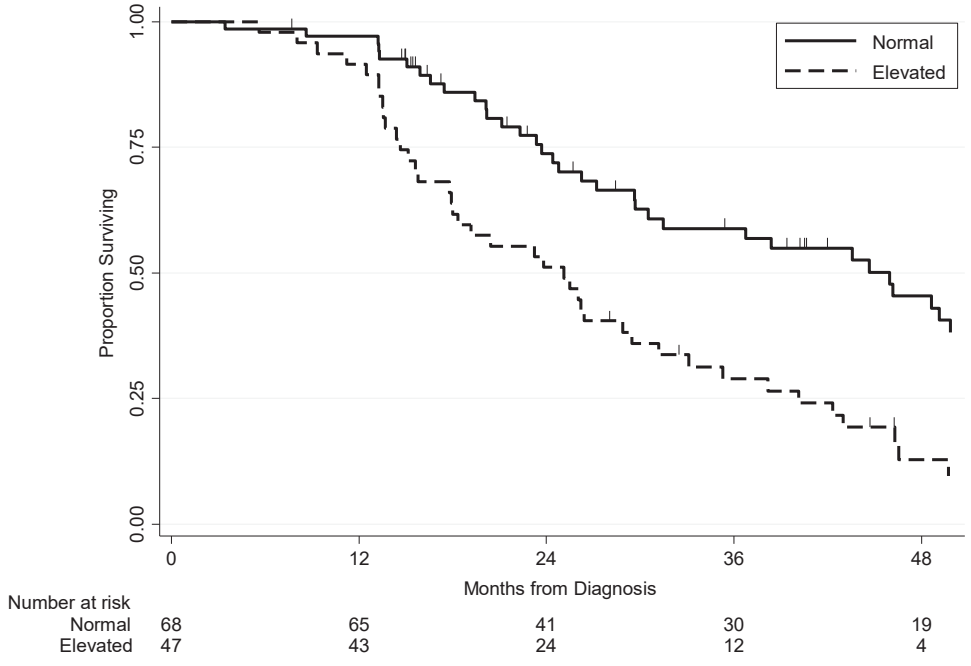

Fig 3. Kaplan-Meier estimates of overall survival by preoperative (postneoadjuvant therapy) CA19-9 for patients who completed all intended neoadjuvant therapy and surgery. The median overall survival of patients with a normal preoperative CA19-9 (*solid line*) was 46 months as compared with 25 months for patients with an elevated preoperative CA19-9 (*dashed line*; $P = .003$).

successful resection (72% vs 67%) in those who received FOLFIRINOX.[21] In the single institution retrospective report by Ferrone et al, neoadjuvant FOLFIRINOX compared with upfront surgery was associated with a decreased risk of lymph node positivity (35% vs 79%), perineural invasion (72% vs 95%), perioperative morbidity (36% vs 63%), and positive margins (8% vs 14%).[22] The authors went on to suggest that following NeoTx with FOLFIRINOX, traditional imaging criteria used to determine resectability was often inaccurate in distinguishing treatment-associated fibrosis from invasive cancer. They concluded that surgical exploration for assessment of resectability should be more liberally applied. Perhaps a better way to explain this clinical observation is that preoperative imaging cannot determine whether the autonomic perineural tissue or sheath (which surrounds visceral arteries; CA, SMA, CHA) is separable from the adventitia of the artery. If separable, the tumor can be removed without arterial resection and reconstruction. However, this is not always possible, and to our knowledge, there is no way to know this before beginning the arterial dissection. If this plane (between

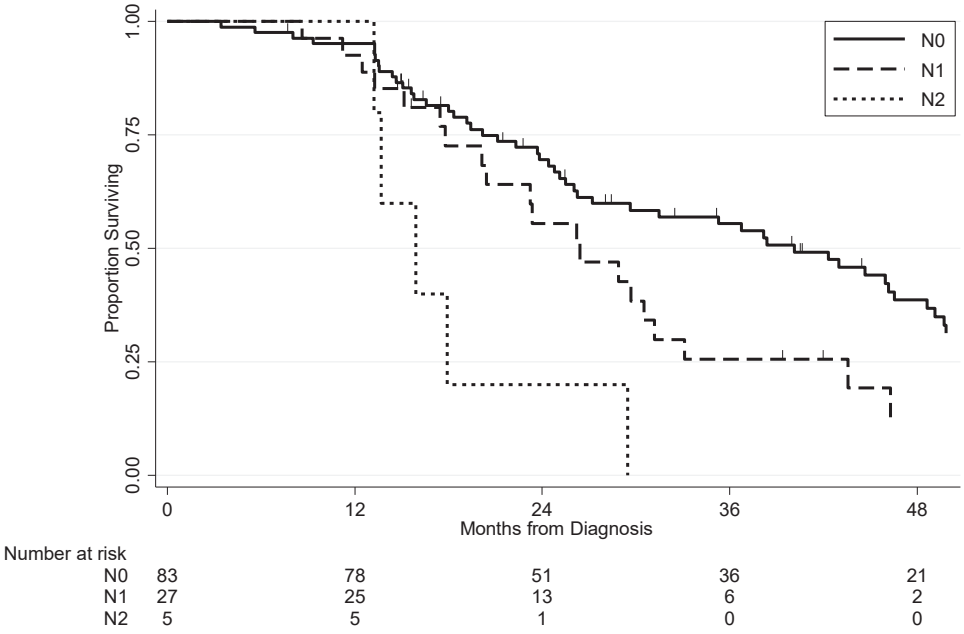

Fig 4. Kaplan-Meier estimates of overall survival by lymph node status for patients who completed all intended neoadjuvant therapy and surgery. The median overall survival of patients with N0 disease (solid line) was 40 months compared with 26 months for patients with N1 disease (dashed line) and 16 months of patients with N2 disease (dotted line; $P = .03$).

Table V
Cox proportional hazards analysis for resected patients only

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age						
≤65 y		Ref.				
>65 y	1.09	0.70–1.70	.37	—	—	—
Sex						
Female		Ref.			Ref.	
Male	1.82	1.16–2.86	.01	1.82	1.13–2.94	.01
Charlson Comorbidity Index						
≤5		Ref.				
>5	1.20	0.74–1.95	.46	—	—	—
Preoperative CA19-9						
≤35 U/mL		Ref.			Ref.	
>35 U/mL	2.26	1.44–3.54	<.001	1.86	1.16–2.99	.01
Vein resection						
No		Ref.			Ref.	
Yes	1.82	1.17–2.84	.01	1.57	0.95–2.60	.08
Artery resection						
No		Ref.				
Yes	1.19	0.55–2.60	.66	—	—	—
T stage						
T0		Ref.			Ref.	
T1	2.20	0.51–9.53	.29	1.68	0.37–7.71	.51
T2	2.99	0.72–12.37	.13	1.40	0.30–6.50	.66
T3	3.22	0.74–13.89	.12	1.50	0.31–7.29	.61
N stage (ref. N0)						
N0		Ref.			Ref.	
N1	1.85	1.12–3.06	.02	1.70	1.00–2.88	.05
N2	4.97	1.92–12.84	.001	4.79	1.75–13.11	.002
Perineural invasion						
No		Ref.			Ref.	
Yes	1.48	0.94–2.33	.09	1.33	0.81–2.21	.26

Ref, reference group.

adventitia and nerve) cannot be developed, the artery needs to be resected. Assuming that the artery can always be separated from the nerve is a mistake. Therefore, in the setting of arterial abutment or encasement, surgery should only be considered if the surgeon has the ability to safely perform vascular resection and reconstruction.[23]

Removal of the involved perineurium is a critical component of an optimal operation because perineural invasion has been found in 80% to 100% of surgical specimens treated with upfront surgery.[24–27] The presence of perineural invasion results in a 1.68-fold increased risk of death and a 2.53% increased risk of disease

Table VI
Preoperative or postoperative CA19-9 and nodal status of resected patients ($n = 115$)

	NmL postoperative CA19-9 (n = 79)	Elev postoperative CA19-9 (n = 31)	LN negative (n = 83)	LN positive (n = 32)
Nml preoperative CA19-9 ($n = 68$)	59 (75%)	5 (16%)	52 (63%)	16 (50%)
Elev preoperative CA19-9 ($n = 47$)	20 (25%)	26 (84%)	31 (37%)	16 (50%)

Missing postoperative CA19-9 values in 5 patients.
Elev, elevated; *Nml*, normal.

progression.[25] However, where the surgeon decides to begin and end the neural resection (both longitudinal and circumferential) is a subjective intraoperative assessment. Therefore, a microscopically positive margin may occur (visible or not apparent under the microscope) even when the operation is performed perfectly. For this reason, local disease recurrence in periarterial neural tissue becomes an increasing common form of disease recurrence in those patients who escape distant disease recurrence.[28] It is thought that neural tissue is infiltrated by the tumor early in carcinogenesis and may be a privileged site for tumor growth and extension. Preoperative chemoradiation is one way to potentially decrease local recurrence rates.[29,30] In patients with BLR PC, chemoradiation has been shown to improve R0 resection rates—something that will translate into improved survival only in those patients who do not die of distant recurrence; hence, the challenge in demonstrating an overall survival benefit from this or any other local therapy.[31,32] The low incidence of local recurrence reported herein is especially impressive given the favorable median survival—patients with isolated local recurrence have a long disease-free interval (median of over 2 years). It is logical to conclude that some patients who experience isolated local recurrence may have been cured with improved local therapy.

Perhaps most promising in our quest to select out which patients are best suited to undergo potentially high-risk surgery for BLR PC is the recent data demonstrating that normalization of CA19-9 after NeoTx is predictive of prolonged survival.[33,34] CA19-9 is a sialylated Lewis antigen and high pretreatment levels are known to be associated with advanced PC and poor survival.[35] Although a decline in CA19-9 may also occur after successful surgery (and if it occurs, it is associated with improved OS), such a decline is not experienced by all operated patients.[36] Therefore, normalization of preoperative CA19-9 is an attractive goal, especially in high-risk patients who require a complex operation. After NeoTx, the current standard for proceeding with surgery is the absence of disease progression as opposed to the presence of treatment response. This inability to accurately assess treatment response is likely responsible for early postoperative recurrence in those who receive NeoTx.[37] CA19-9, when used as a treatment response biomarker during NeoTx, correlates with otherwise unmeasurable changes in disease response. Both the normalization of preop and postop CA19-9 were associated with a doubling of OS in a recent report from our institution consistent with the findings reported.[37] The future of neoadjuvant treatment sequencing will incorporate an adaptive design that utilizes a variety of biomarkers (CA19-9, circulating tumor cells, etc) and radiographic techniques (novel PET and MRI techniques, etc) to define response early within a treatment program.[38] Equally important will be the ability to better match the individual host and tumor characteristics with optimal systemic therapy at the time of diagnosis. Our initial experience with tumor profiling based on endoscopic ultrasound with fine-needle aspiration biopsies has developed the needed infrastructure for the more widespread application of this technology.[12] For example, our initial work with preoperative molecular profiling can be expanded to include targeted genomic analysis of the distinct subtypes of PC.[39,40] Personalized treatments of maximal efficacy are being combined with rapid assessment of response and a treatment duration which minimizes cumulative toxicities. These novel advances in NeoTx sequencing will facilitate a safer operation as we move to a total neoadjuvant approach for patients with operable PC to include those with resectable disease.[12,14,15,37,41,42] The need to minimize cumulative toxicities and balance the competing influences of treatment duration and response can only be appreciated from an intent-to-treat analysis of all patients censored at the time of initial staging (at the time of diagnosis). Reports that highlight the results of just those patients who successfully complete all intended primary therapy (chemotherapy and surgery in any order) are prone to a tremendous selection bias.[43,44] Such data can encourage the development of inflexible treatment plans, which may have a duration and toxicity profile inappropriate for many patients with localized pancreatic cancer whose age and comorbidities may warrant a more tailored approach.

Our study illustrates the work that still needs to be done in improving the care of patients with BLR PC. The patients included in this report were not part of any prior or ongoing in-house clinical trials and have not been previously reported; they represent an unselected population of newly diagnosed patients. Limitations of this study include its single institution retrospective design with potential for associated biases owing to variations in the treatments delivered. Of the 185 patients with BLR PC who initiated treatment with curative intent, 115 (62%) completed all intended NeoTx and surgery; a number lower than reported in a recent clinical trial owing to the absence of any restrictions on treatment other than physician judgment.[12] Current and future efforts in NeoTx sequencing at our institution are focused on developing the optimal treatment for each patient as their first treatment and the early identification of nonresponding patients and mechanisms to rapidly adjust therapy. Importantly, of those who completed all intended NeoTx and surgery, 72% were node negative and 97% had R0 margins. Median OS of all patients was 20 months, similar to the survival of consecutive patients who receive surgery first as reported from single institution experiences.[45] The median OS was 31 months for those who completed all intended therapy and over 40 months for those who normalized their CA19-9 before surgery or had node negative disease (Table VI); numbers that rival the survival of patients with resectable PC.[14] As we have advocated for many years, 3 factors should be carefully assessed in all patients before surgery for localized PC: the complexity of surgery, the general risk for the patient (age and comorbidities), and the oncologic profile (response to induction therapy). We do not operate on a high-risk patient who needs a complex operation in the setting of an unfavorable oncologic profile.

In conclusion, after NeoTx, surgical resection was performed in 62% of patients with BLR PC. Those patients who normalized preoperative CA19-9 or were node negative on final pathology achieved the longest median survival. Initial therapy based on molecular profiling combined with adaptive approaches to induction therapy (based on objective assessment of response) will optimize the survival of all patients with localized, potentially operable PC.

Disclosure

The authors have no personal conflicts of interest.

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