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Pathologic tumor response to neoadjuvant therapy in borderline resectable pancreatic cancer

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ABSTRACT

Background: Previous studies have demonstrated the prognostic significance of pathologic tumor response in pancreatic adenocarcinoma following neoadjuvant therapy (NAT). The aim of this study was to determine the incidence of significant pathologic response to NAT in borderline resectable pancreatic cancer (BRPC), and association of NAT regimen and other clinico-pathologic characteristics with pathologic response.

Methods: Patients with BRPC who underwent NAT and pancreatic resection between January 2012 and June 2017 were included. Pathologic response was assessed on a qualitative scale based on the College of American Pathologists grading system. Demographics and baseline characteristics, oncologic treatment, pathology, and survival outcomes were compared.

Results: Seventy-one patients were included for analysis. Four patients had complete pathologic responses (tumor regression score 0), 12 patients had marked responses (score 1), 42 had moderate responses (score 2), and 13 had minimal responses (score 3). Patients with complete or marked responses were more likely to have received neoadjuvant gemcitabine chemoradiation (62.5%, 38.1%, and 23.1% of the complete/marked, moderate, and minimal response groups, respectively; $P = 0.04$). Of the complete/marked, moderate, and minimal response groups, margins were negative in 75.0%, 78.6%, and 46.2% ($P = 0.16$); node negative disease was observed in 87.5%, 54.8%, and 15.4% ($P < 0.01$); and median overall survival was 50.0 months, 31.7 months, and 23.2 months ($P = 0.563$). Of the four patients with pathologic complete responses, three were disease-free at 66.1, 41.7 and 31.4 months, and one was deceased with metastatic liver disease at 16.9 months.

Conclusions: A more pronounced pathologic tumor response to NAT in BRPC is correlated with node negative disease, but was not associated with a statistically significant survival benefit in this study.

Introduction

The overall prognosis of pancreatic cancer remains poor despite gains made with multimodality therapy [1,2]. Approximately 45% of newly diagnosed patients present with metastatic disease, and 41.4% of patients without radiographic evidence of metastases can have unresectable disease at exploration [3,4]. This propensity for overt and occult metastatic potential has led many centers to utilize neoadjuvant therapy (NAT) for borderline resectable and locally advanced pancreatic cancer (BRPC, LAPC) to improve local resectability and treat systemic micrometastatic disease. NAT is now part of the algorithm for BRPC recommended by the National Comprehensive Cancer Network (NCCN) [5–7].

Radiographic downstaging of BRPC after NAT is uncommon and is not required for an attempt for resection, as radiographic response is not predictive of improved survival [8]. Patients in a combined resectable and BRPC cohort with complete or marked response after NAT were shown in a recent retrospective study to have improved survival [9].

Our preferred approach in BRPC is neoadjuvant chemoradiation followed by surgical resection. The aim of this study was to determine the prevalence of significant pathologic response and elucidate whether degree of response correlates with improved outcome.

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Methods

This retrospective study was performed with approval from the Institutional Review Board. Patients with BRPC who underwent NAT and partial or total pancreatectomy from January 2012 to June 2017 were identified from an institutional pancreatectomy database.

Patient selection and neoadjuvant pathway

BRPC was defined by NCCN criteria [5]. This definition included head and uncinate tumors with less than 180° contact with the superior mesenteric artery, superior mesenteric or portal vein irregularity or thrombosis, or more than 180° contact with the vein. For tumors of the body and tail, borderline resectable lesions included those with less than 180° contact with the celiac axis, or > 180° contact of the celiac axis without involvement of the aorta or gastroduodenal artery.

A clinical pathway was in place at our institution for patients treated for BRPC during the time period of this study, but deviations were allowed at the discretion of the surgical or medical oncologist. All treated patients had biopsy proven adenocarcinoma of the pancreas and thin cut pancreatic protocol computed tomography (CT) demonstrating borderline resectability as defined by NCCN. Patient imaging and history were routinely reviewed prior to and after NAT at a weekly multidisciplinary tumor board. The clinical pathway included staging diagnostic laparoscopy (SDL) with peritoneal washings for cytology prior to NAT to rule out radiographically occult metastatic disease. Neoadjuvant chemoradiation was the preferred regimen, with 50.4–56.0 cGy of external beam radiation administered in 28 fractions, and concurrent administration of a radiosensitizing agent such as gemcitabine, 5-fluorouracil (5-FU), or capecitabine. Restaging CT was performed four to six weeks after completion of NAT. Patients with stable local disease and no evidence of metastatic disease were scheduled for resection.

Preprocedure diagnostic laparoscopy was repeated at the time of resection to exclude occult metastatic disease. Patients underwent pancreatoduodenectomy (PD), distal pancreatectomy (DP), or total pancreatectomy (TP) depending on the location of the cancer. Intraoperative frozen section was obtained for the pancreatic duct margin for PD's and DP's, and bile duct margins were checked for PD's. In general, additional margins were excised if adenocarcinoma was noted on frozen section, although the decision for further resection was at the discretion of the surgeon. Vascular resection was performed based on intraoperative suspicion of tumor involvement. The superior mesenteric and portal vein margin, and the superior mesenteric artery groove were inked by the surgeon in the operating room.

Pathologic evaluation

Surgical specimens were grossed following standard multivalve technique, and lymph nodes were examined using the orange-peeling technique [10]. Final pathologic examination was reported using the College of American Pathologists (CAP) "Protocol for the examination of specimens from patients with carcinoma of the pancreas" [11]. Treatment effect was assessed using the tumor regression score as follows: score of 0 for complete response with "no viable cancer cells," a score of 1 for near complete response with "single cells or rare small groups of cancer cells," a score of 2 for partial response with tumor regression but "more than single cells or rare groups of cancer cells," and a score of 3 for poor or no response with "extensive residual cancer with no evident tumor regression" [11]. Patients without grading of pathologic tumor response were excluded from analysis. Pathologic margins were considered negative for this study if tumor was at least 1 mm from inked margins.

Adjuvant therapy and surveillance

Adjuvant therapy was routinely recommended and during the time period of this study was comprised primarily of gemcitabine monotherapy. Surveillance was performed generally following the NCCN guidelines [5]. Tissue confirmation of suspected recurrence was not required, and palliative chemotherapy was administered based on discussion between each individual patient and their medical oncologist.

Data acquisition and analysis

Data on patient demographics, chemotherapy and radiation regimens, pathology, and oncologic outcomes were obtained from a prospectively collected database, supplemented with review of the electronic medical record. Survival data were supplemented with public domain death registration data. Disease-free survival (DFS) was calculated from the date of surgical resection to date of recurrence or death if no recurrence was documented. Overall survival (OS) was calculated from the date of diagnosis to date of death. Patients who were lost to follow-up were censored at the time of last normal imaging or history and physical examination for DFS and last interaction within the institution's medical record for OS.

Continuous variables were described using means and standard deviations (SD), and categorical variables were described using counts and percentages. Chi-square, Fisher's exact, and one-way analysis of variance (ANOVA) tests were used to perform comparisons. Survival curves were estimated using the Kaplan–Meier method and differences were compared using the log-rank test. Two-sided P values were used with a significance level of 0.05. All analyses were performed using R software (version 3.3.1, Vienna, Austria).

Results

A total of 71 patients were identified for inclusion. PCR was observed in 4 patients (5.6%), marked response in 12 patients (16.9%), moderate response in 42 patients (59.2%), and minimal response in 13 patients (18.3%). Due to low numbers, the complete and marked response groups were combined for analysis.

Patient characteristics and treatment

Demographic characteristics, neoadjuvant and adjuvant treatment regimens, and recurrence data are summarized in Table 1. The three groups were of comparable age, sex, and body mass index. There were no differences in preoperative carbohydrate antigen 19-9 (CA 19-9) or albumin levels. NAT consisted of concurrent chemoradiation for 56 patients, chemotherapy for 9 patients, and a sequential treatment of chemotherapy and chemoradiation for 6 patients. The majority of patients underwent pancreatoduodenectomy and approximately one-third of patients required vein resection during surgery. The median operative time for all patients was 406 min [interquartile range (IQR) 337–453], estimated blood loss was 350 mL (IQR 250–700), and length of stay was 7 days (IQR 5–8). Chemoradiation using gemcitabine as a radiosensitizer was associated with increased complete and marked response rate. Adjuvant chemotherapy administered in 49 patients (69.0%), comprised most commonly of gemcitabine monotherapy ($n = 38$) or in combination with capecitabine ($n = 3$). The most common site of first recurrence was distant recurrence in all groups.

Table 1
Demographics, treatment, and recurrence.

Variables	All patients ($n = 71$)	Complete or marked response ($n = 16$)	Moderate response ($n = 42$)	Minimal response ($n = 13$)	*P* value
Age (yr)	64.1 ± 11.0	63.2 ± 11.8	63.8 ± 10.0	66.2 ± 13.7	0.75
Sex					
Male	41 (57.7%)	10 (62.5%)	23 (54.8%)	8 (61.5%)	0.83
Female	30 (42.3%)	6 (37.5%)	19 (45.2%)	5 (38.5%)	
Body mass index (kg/m²)	26.4 ± 4.9	25.4 ± 4.0	27.3 ± 5.3	24.8 ± 4.1	0.20
Preoperative CA 19-9 (U/mL)	575 ± 1164	377 ± 401	630 ± 1414	573 ± 651	0.84
Preoperative albumin (g/dL)	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	0.97
Post NAT albumin (g/dL)	3.8 ± 0.5	3.9 ± 0.4	3.9 ± 0.5	3.8 ± 0.7	0.91
NAT					
Chemoradiation					**0.04**
Gemcitabine	28 (39.4%)	10 (62.5%)	15 (35.7%)	3 (23.1%)	
5-FU	4 (5.6%)	1 (6.3%)	2 (4.8%)	1 (7.7%)	
Capecitabine	22 (31.0%)	4 (25.0%)	16 (38.1%)	2 (15.4%)	
Other	2 (2.8%)	1 (6.3%)	0	1 (7.7%)	
Other regimen	15 (21.1%)	0	9 (21.4%)	6 (46.2%)	
Operation					0.09
Pancreatoduodenectomy	49 (69.0%)	13 (81.3%)	31 (73.8%)	5 (38.5%)	
Distal pancreatectomy	19 (26.8%)	3 (18.8%)	9 (21.4%)	7 (53.9%)	
Total pancreatectomy	3 (4.2%)	0	2 (4.8%)	1 (7.7%)	
Vein Resection	24 (33.8%)	3 (18.8%)	18 (42.9%)	3 (23.1%)	0.17
Adjuvant therapy					0.63
Yes	49 (69.0%)	12 (75.0%)	30 (71.4%)	7 (53.8%)	
No	13 (18.3%)	2 (12.5%)	8 (19.0%)	3 (23.1%)	
Unknown	9 (12.7%)	2 (12.5%)	4 (9.5%)	3 (23.1%)	
First recurrence					0.21
Local	8 (11.3%)	3 (18.8%)	5 (11.9%)	0	
Distant	26 (36.6%)	7 (43.8%)	13 (31.0%)	6 (46.2%)	
Death without recurrence	28 (39.4%)	6 (37.5%)	19 (45.2%)	3 (23.1%)	
No recurrence	6 (8.5%)	0	4 (9.5%)	2 (15.4%)	
Unknown	3 (4.2%)	0	1 (2.4%)	2 (15.4%)	

CA 19-9: carbohydrate antigen 19-9; NAT: neoadjuvant therapy; 5-FU: 5-fluorouracil.

Table 2
Pathology.

Variables	All patients ($n = 71$)	Complete or marked response ($n = 16$)	Moderate response ($n = 42$)	Minimal response ($n = 13$)	*P* value
Tumor size (cm)	3.1 ± 1.5	2.4 ± 1.4	3.2 ± 1.5	3.4 ± 1.1	0.12
Tumor grade					
1	9 (12.7%)	0	7 (16.7%)	2 (15.4%)	<**0.01**
2	37 (52.1%)	7 (43.8%)	24 (57.1%)	6 (46.2%)	
3	18 (25.4%)	2 (12.5%)	11 (26.2%)	5 (38.5%)	
Cannot assess	7 (9.9%)	7 (43.8%)	0	0	
Margin	51 (71.8%)	12 (75.0%)	33 (78.6%)	6 (46.2%)	0.16
R0	20 (28.2%)	4 (25.0%)	9 (21.4%)	7 (53.8%)	
R1					
LVI	42 (59.2%)	3 (18.8%)	26 (61.9%)	12 (92.3%)	<**0.01**
PNI	59 (83.1%)	9 (56.3%)	38 (90.5%)	12 (92.3%)	**0.01**
T stage	4 (5.6%)	4 (25.0%)	0	0	0.07
No residual tumor	6 (8.5%)	2 (12.5%)	3 (7.1%)	1 (7.7%)	
T1	8 (11.3%)	2 (12.5%)	5 (11.9%)	1 (7.7%)	
T2	48 (67.6%)	7 (43.8%)	31 (73.8%)	10 (76.9%)	
T3	5 (7.0%)	1 (6.3%)	3 (7.1%)	1 (7.7%)	
T4					
N stage	39 (54.9%)	14 (87.5%)	23 (54.8%)	2 (15.4%)	<**0.01**
N0	32 (45.1%)	2 (12.5%)	19 (45.2%)	11 (84.6%)	
N1					
≥ 12 nodes harvested	59 (83.1%)	13 (81.3%)	36 (85.7%)	10 (76.9%)	0.68

LVI: lymphovascular invasion; PNI: perineural invasion.

Pathologic outcomes

Histopathologic outcomes are summarized in Table 2. Tumor differentiation was reported for all patients except 7 of those with marked or complete response due to paucity of viable tumor cells available for evaluation. Margins were negative in 51 patients (71.8%), without significant correlation with degree of treatment response. However, the complete/marked response group were statistically less likely to have lymphovascular invasion (18.8%, 61.9%, and 92.3% in the complete/marked, moderate, and minimal response groups, respectively; $P < 0.01$), perineural invasion (56.3%, 90.5%, and 92.3%; $P = 0.01$), and node positive disease (12.5%, 45.2%, and 84.6%; $P < 0.01$). At least 12 lymph nodes were harvested in 59 patients (83.1%) with no difference in nodal yield between the three groups.

Comparison of neoadjuvant regimens

Because analysis demonstrated that a greater proportion of patients with a favorable pathologic response received gemcitabine chemoradiation, additional analysis was performed to compare patients who underwent gemcitabine chemoradiation versus 5-FU or capecitabine chemoradiation, with results shown in Table 3. There were no differences in baseline characteristics or preoperative CA

Table 3
Gemcitabine versus 5-fluorouracil/capecitabine chemoradiation (*n*, %).

Characteristics	Gemcitabine ($n = 30$)	5-FU/capecitabine ($n = 27$)	*P* value
Age (yr)	66.8 ± 9.8	63.0 ± 11.9	0.19
Male sex	19 (63.3%)	15 (55.6%)	0.60
Body mass index (kg/m^2)	27.1 ± 4.9	26.5 ± 5.1	0.67
CA 19-9 (U/mL)			
Presenting	611.8 ± 1621.2	415.9 ± 571.0	0.58
Post NAT	122.5 ± 204.1	121.8 ± 131.0	0.99
Pathology			
Tumor size (cm)	3.3 ± 1.6	3.0 ± 1.4	0.53
Treatment response			0.24
Complete or marked	10 (33.3%)	5 (18.5%)	
Moderate or minimal	20 (66.7%)	22 (81.5%)	
Margin negative	22 (73.3%)	21 (77.8%)	0.99
LVI	14 (46.7%)	15 (55.6%)	0.69
PNI	23 (76.7%)	22 (81.5%)	0.91
T stage			0.32
No residual tumor	4 (13.3%)	0	
T1	2 (6.7%)	1 (3.7%)	
T2	3 (10.0%)	5 (18.5%)	
T3	19 (63.3%)	19 (70.4%)	
T4	2 (6.7%)	2 (7.4%)	
N stage			**0.01**
N0	24 (80.0%)	11 (40.7%)	
N1	6 (20.0%)	16 (59.3%)	
≥ 12 nodes harvested	23 (76.7%)	23 (85.2%)	0.51
Disease-free survival (mon, median)	14.3	15.5	0.61*
Overall survival (mon, median)	26.5	29.2	0.61*

* : Disease-free and overall survival were compared using the log-rank test. CA 19-9: carbohydrate antigen 19-9; NAT: neoadjuvant therapy; 5-FU: 5-fluorouracil; LVI: lymphovascular invasion; PNI: perineural invasion.

19-9 levels. Gemcitabine chemoradiation was associated with more node negative disease, but no other differences in pathologic outcomes or survival.

Survival outcomes

Survival outcomes were analyzed and demonstrated no statistically significant differences between the three groups. Median DFS was 22.3 months, 14.3 months, and 15.2 months for the complete/marked, moderate, and minimal response groups, respectively ($P = 0.423$, Fig. 1A). Median OS was 50.0 months, 31.7 months, and 23.2 months ($P = 0.563$, Fig. 1B). Median follow-up time was 19.8 months (range 3.6 to 70.8 months).

There were four patients with PCR after NAT. All received gemcitabine chemoradiation and underwent pancreatoduodenectomy without vein resection. Three of four patients were alive and disease-free at 66.1 months, 41.7 months and 31.4 months, respectively, and one expired with metastatic disease to the liver at 16.9 months.

Discussion

There has been increasing interest in the use of NAT in pancreatic cancer, especially for BRPC and LAPC. NAT treats systemic micrometastatic disease, allows the tumor biology to become apparent, and provides local control which enables margin-negative resection while avoiding vascular resection.

NAT has been commonly used in other locally advanced malignancies, such as esophageal and rectal cancers, where a PCR is highly significant [12–14]. In a series of 235 patients with clinical stage II and higher esophageal cancer, 33% of patients had a PCR in the primary tumor after chemoradiation, and post-therapy stage was a strong independent predictor of improved OS [12,13]. The PCR rate in rectal cancer has been reported from 8%–24% depending on initial clinical stage and patients with PCR had improved DFS and OS compared to patients with residual disease despite being less likely to undergo adjuvant chemotherapy [14], which has prompted use of a "wait-and-see" approach for patients with clinical complete response after NAT with successful avoidance of surgery in 50% [15,16].

In pancreatic cancer, especially in BRPC, NAT can select patients who benefit from surgery by identifying those with metastatic disease or comorbidities that would preclude surgery. Our prior experience of 100 patients with BRPC eligible for NAT and resection showed that 38 patients ultimately proceeded to operative exploration and 26 patients underwent resection [17]. Pretherapy staging diagnostic laparoscopy identified metastatic disease in 25.3% of patients. For patients who started NAT, 39.2% progressed and 12.7% dropped out due to poor tolerance or complications during NAT. The significantly lower resection rate compared to initial rate of 68% reported by the Alliance A021101 trial [18] may be due to less stringent criteria for patient inclusion in treatment.

The rise of NAT in borderline and resectable pancreatic cancer brings challenges in our understanding the prognostic significance of post-therapy pathology. This study was comprised of only BRPC patients and demonstrated a PCR in 5.6% of patients and near complete response in another 16.9% of patients. We found that patients who underwent gemcitabine chemoradiation had a more favorable pathologic response compared to other neoadjuvant regimens used in this study. Amongst those who received gemcitabine chemoradiation, the PCR rate was 4 of 29 (13.8%) and marked response in another 6 patients (20.7%). A more pronounced treatment effect was associated with other favorable characteristics including less nodal disease, perineural invasion (PNI), and lymphovascular invasion (LVI). There was a trend toward improved OS with a complete or marked pathologic response, but the difference did not reach statistical significance in our study (median 50.0 months in complete or marked response versus 23.2 months in minimal response, $P = 0.563$). The lack of statistical significance is probably due to the small sample size but is likely clinically significant. Another potential consideration for lack of survival advantage in responders is that pancreatic cancer is often a systemic disease and therefore, chemoradiation alone as a locoregional therapy might not offer survival benefit even if pathologic outcomes are improved,

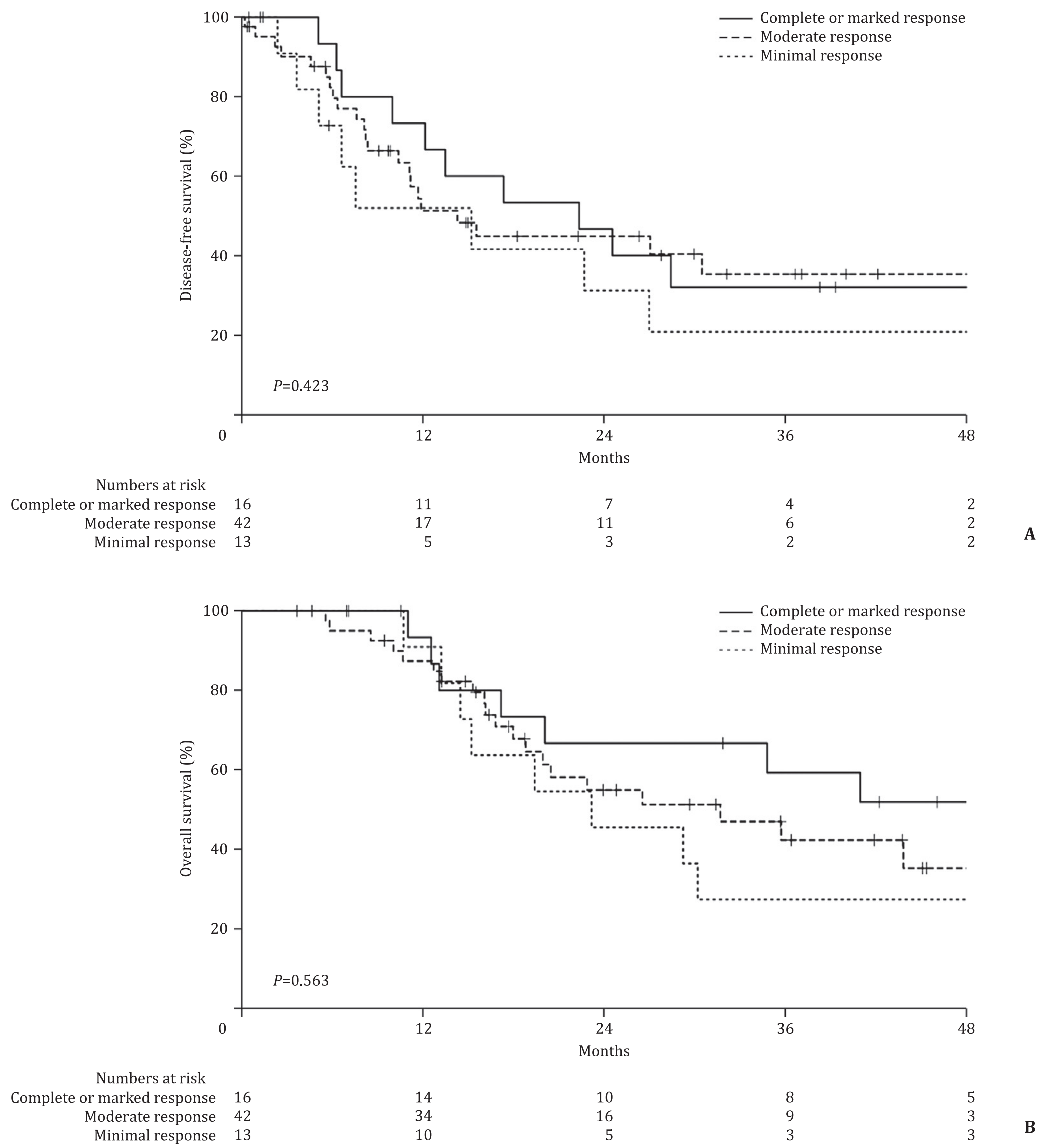

Fig. 1. Kaplan–Meier survival curves for disease-free survival (**A**) and overall survival (**B**). Censored patients are marked by hashmarks.

especially in BRPC patients who are at higher risk for occult metastatic disease. However, since a similar percentage of patients in each response group received adjuvant systemic chemotherapy and the rates of local versus systemic recurrence were similar between groups, it is difficult to separate the survival impact of the local versus systemic treatment in our patients. During the time period of this study, no patient underwent multidrug regimens such as 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX).

The impact of NAT and the implications for prognosis have been reported previously for combined groups of potentially resectable and LAPC. An analysis of 583 patients with resectable, borderline resectable, and locally advanced disease undergoing NAT demonstrated a PCR of 3.9% with another 9.3% achieving a marked response [9]. Multivariable analysis identified gemcitabine chemoradiation, age less than 50 years, and CA 19-9 level less than 200 U/mL as factors associated with a complete or marked pathologic response. BRPC represented 110 of the patients in this series, with 12.7% experiencing complete or marked response [9], slightly lower than 22.5% in the current study, although both studies highlighted the benefit of gemcitabine chemoradiation. The complete/marked response group in that study had a more favorable survival at 73.4 months compared to 32.2 months in the remaining patients ($P < 0.001$). The better survival in both groups reported by Cloyd et al. [9] compared to the current study is likely due to enrichment of their study in patients with resectable disease.

Several smaller studies have noted PCR in surgical specimens after various combinations of chemotherapy and chemoradiation in BRPC [18–20] and LAPC [20–22]. Treatment using FOLFIRINOX has shown improved survival in the metastatic setting [23] and recently in the adjuvant setting [24], and is under study for BRPC and LAPC in the neoadjuvant setting. Preliminary reports from the Alliance trial which includes FOLFIRINOX followed by capecitabine chemoradiation in BRPC indicated a PCR in 2 of 15 patients (13.3%) and marked response in another 3 patients (20.0%) [18], similar to the 34.5% of patients undergoing gemcitabine chemoradiation in the current study. Likewise, a systematic review of FOLFIRINOX-based regimens in LAPC noted a PCR in 6 of 85 patients (7.1%) [25].

Although OS in this study showed a difference of almost 27 months between the complete/marked response and minimal response groups, this difference was not statistically significant likely due to the limited sample size. Data from prior studies and confirmation of improved pathologic outcomes with decreased nodal disease, LVI, and PNI in our study all suggest that the survival benefit in the complete/marked response group is clinically significant.

In conclusions, marked or CRP were seen in 22.5% of our cohort who underwent NAT for BRPC, and 34.5% of patients who underwent gemcitabine chemoradiation. Both the current and previous studies suggest that gemcitabine chemoradiation has the highest rate of significant response. Complete or marked pathologic response in BRPC is associated with less nodal disease, PNI, and LVI, with a trend towards prolonged OS.

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Contributors

PJS, WJ, CS and MG proposed the study. PJS, WJ, CS, ADS, and MG performed the research. PJS wrote the first draft. PJS collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. MG is the guarantor.

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Ethical approval

This retrospective study was performed with approval from the Institutional Review Board.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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