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ORIGINAL ARTICLE – PANCREATIC TUMORS

Preoperative Capecitabine and Concurrent Radiation for Borderline Resectable Pancreatic Cancer

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ABSTRACT

Background. Patients with borderline resectable pancreatic ductal adenocarcinoma (PDA) represent a high-risk group of patients due to tumor or patient-related characteristics. The optimal management of these patients has not been fully defined.

Materials and Methods. All patients undergoing evaluation for PDA between 2005 and 2008 were identified. Clinical, radiographic, and pathological data were retrospectively reviewed. Patients were staged as borderline resectable using the M.D. Anderson Cancer Center (MDACC) classification.

Results. A total of 170 patients with PDA were identified, 40 with borderline resectable disease. Of these, 34 borderline resectable patients (85%) completed neoadjuvant therapy and were restaged; pancreatic resection was completed in 16 patients (46%). Also, 8 patients completed 50 Gy of radiation in 28 fractions in 6 weeks, whereas 8 patients received 50 Gy in 20 fractions in 4 weeks plus chronomodulated capecitabine. An R0 resection was achieved in 12 of the 16 patients (75%). Also, 5 patients (63%) treated in 20 fractions had >90% pathologic response versus 1 (13%) treated in 28 fractions ($P < .05$). Borderline resectable patients completing surgery had similar survival to patients with resectable disease who underwent surgery. Patients receiving accelerated fractionation radiation had improved survival compared with patients treated with standard fractionation protocol.

Conclusions. A neoadjuvant approach to borderline resectable PDA identifies patients who are most likely to benefit from pancreatic resection. Preoperative capecitabine-based chemoradiation is an effective, well-tolerated treatment for these patients. Neoadjuvant therapy for borderline resectable PDA warrants further investigation using treatment schedules that can safely intensify irradiation dose.

Pancreatic ductal adenocarcinoma (PDA) remains a significant health concern in the United States. Second only to colon cancer, PDA is an extremely lethal gastrointestinal malignancy with an estimated incidence of 37,000 new cases resulting in nearly 34,000 deaths and an overall median survival of 5–6 months.[1]

Early diagnosis followed by multimodality therapy is essential to achieving long-term survival in patients with PDA. Patients presenting with surgically resectable disease (stages I and II) and undergoing a margin-negative (R0) resection may achieve median survival ranging from 12–26 months.[2,3] However, early local infiltration (stage III) and distant metastasis (stage IV) are 2 hallmarks of PDA that preclude 80–85% of patients from undergoing surgery. Patients with locally advanced disease have a significantly higher rate of margin-positive (R1) resection with survival rates similar to patients with locally advanced, unresectable disease.[4–8]

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Strategies aimed at improving R0 resection rates among patients with minimal arterial involvement may provide a significant survival benefit in a group who might otherwise be unresectable. Such a subset of patients with marginally resectable tumors is emerging as a cohort who may benefit from neoadjuvant chemoradiation prior to surgery.[9] These patients are classified as "borderline resectable" based on anatomical tumor involvement of the local vasculature, indeterminate metastatic disease, or temporary poor performance status requiring prolonged evaluation or therapy precluding them from immediate pancreatic resection.[10] Neoadjuvant therapy in this population allows for further stratification of patients with locally invasive disease and the avoidance of a potentially morbid and nonbeneficial operation in patients with suspected metastatic disease or irrecoverable comorbidities.

Ambiguity in borderline resectable PDA classification has limited the development of a standardized treatment scheme with regard to duration, choice of chemotherapy, and use of targeted therapies. Strategies implemented at other institutions have included a dual treatment phase of systemic chemotherapy and chemoradiation with a radiosensitizing agent (e.g., fluorouracil, gemcitabine).[10,11] At our institution, we employ a single treatment phase consisting of chronomodulated capecitabine-based accelerated irradiation followed by clinical and radiologic restaging for determination of candidacy for surgery.

In this study, we report our institutional experience of treating patients with borderline resectable PDA with using neoadjuvant chemoradiation.

METHODS

Institutional review board (IRB) approval was received prior to the initiation of this study. All patients with PDA evaluated at our Surgical Oncology clinics between August 2005 and August 2008 were identified from our prospectively collected database. Patients with an adenocarcinoma arising in an intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasm (MCN) were excluded from this study.

Figure 1a outlines the treatment protocol at our institution. Patients underwent complete preoperative evaluation including clinical history and physical examination, laboratory assessment (complete blood count, chemistry, CA19-9, CEA), and preoperative staging by magnetic resonance imaging (MRI). Histologic confirmation of PDA was performed on tissue obtained by endoscopic ultrasound with fine needle aspiration (EUS/FNA) or endoscopic retrograde cholangiopancreatography (ERCP) with duct brushings.

Following initial evaluation, each patient was reviewed at our multidisciplinary gastrointestinal tumor conference. Patients were defined as potentially resectable, unresectable, or borderline resectable in accordance with the MD Anderson Cancer Center (MDACC) classification scheme.[10] Patients with borderline resectable disease were further characterized into 1 of 3 subtypes (Fig. 2). Patients were classified as subtype A when the tumor abutted the superior mesenteric artery (SMA) or celiac axis, abutted or encased the hepatic artery over a short segment, or caused a resectable short-segment occlusion of the superior mesenteric vein (SMV), portal vein (PV), or SMV-PV confluence with anatomical vascular options suitable for reconstruction. Patients with suspicion for extrapancreatic metastatic disease or known N1 disease were defined as subtype B. Subtype C included patients with severe pre-existing medical comorbidities requiring prolonged evaluation or recovery and precluding immediate surgery. Patients eligible for multiple categories were assigned a single classification in the following hierarchy: subtype C >subtype B >subtype A.

Neoadjuvant Treatment Strategy

Borderline resectable patients were referred for neoadjuvant therapy with external beam radiation (EBR) and concomitant radiation-sensitizing chemotherapy. Patients treated at referring centers received 50.4 Gy in 28 fractions with concurrent capecitabine, while patients treated at our institution received an accelerated protocol consisting of 50 Gy in 20 fractions with concurrent chronomodulated capecitabine based on our institutional experience with chronomodulated techniques. Treatment planning consisted of a computed tomography (CT) scan in the supine position. The treatment planning images were fused with diagnostic CT or MR images for delineation of the gross tumor volume (GTV) consisting of the primary tumor and the immediate draining lymph nodes (not the para-aortic or porta-hepatis regions). The planning tumor volume (PTV) consisted of 0.5–1.5-cm radial and 1–2-cm craniocaudal expansions of the GTV to account for setup error. Patients received 50 Gy in 20 fractions (2.5 Gy/fraction) prescribed to 95% of the PTV via a helical Tomotherapy Hi-Art treatment system. This system uses intensity modulated radiation treatment (IMRT) and image-guided treatment (IGRT) where a megavoltage CT image is obtained prior to each treatment to check for portal alignment. Concurrent chronomodulated oral capecitabine (1 gm, 60 min after the morning meal and 2 gm, 60 min after the evening meal) was administered on each day of irradiation. Patients were evaluated regularly for adverse effects according to the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring criteria.

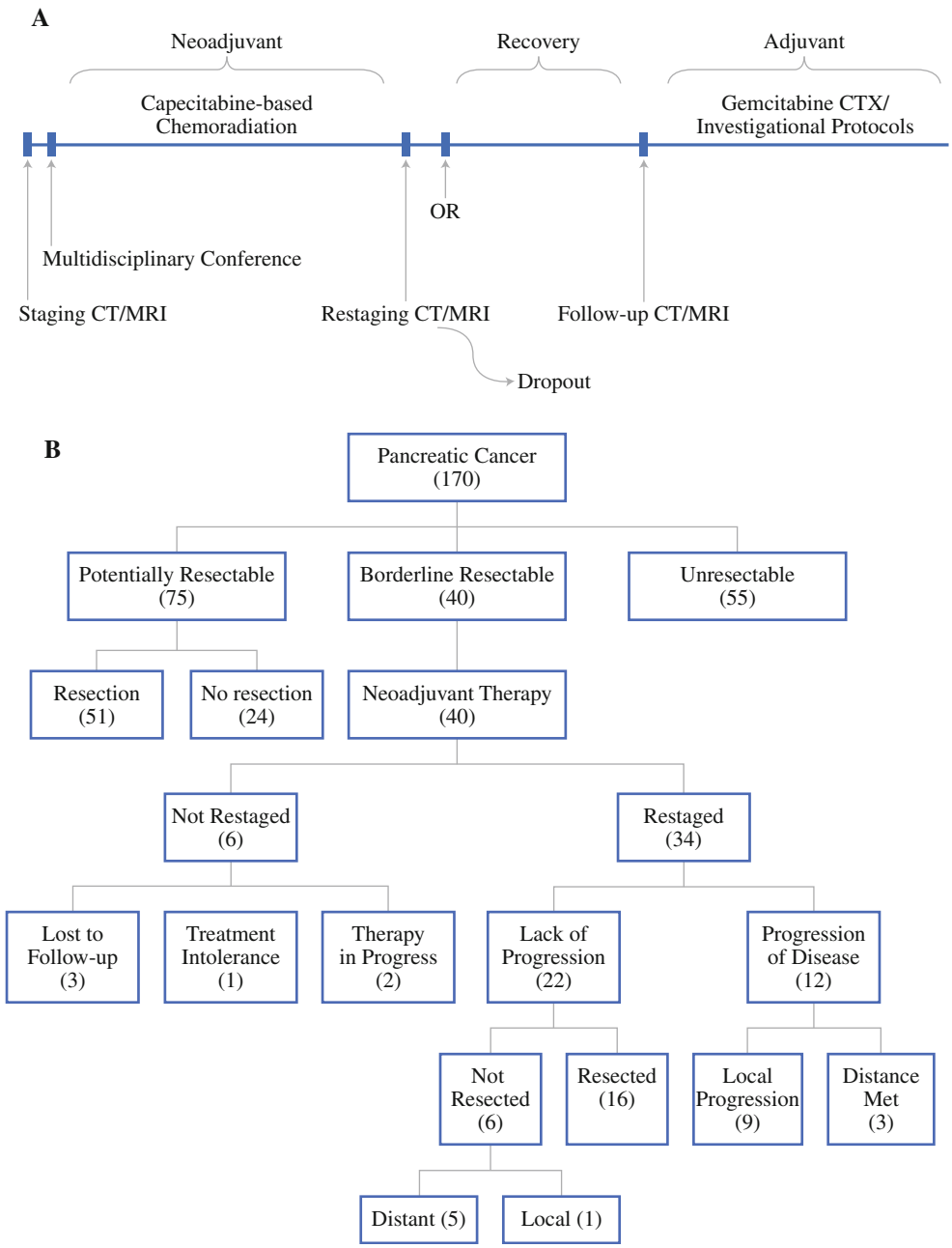

FIG. 1 **a** Treatment strategy for patients with borderline resectable pancreatic cancer. CT, computed tomography; MRI, magnetic resonance imaging; OR, taken to operating room for pancreatic resection; CTX, chemotherapy. **b** Summary of treatment of 170 patients with PDA at our institution during the study period

Following completion of neoadjuvant treatment, patients were reevaluated clinically and underwent MRI of the abdomen, CXR, and serum CA19-9 to evaluate for evidence of tumor progression or metastatic disease. Surgery was then scheduled for patients demonstrating lack of progression of disease and who were determined physiologically suitable. All surgeries were performed at our institution by 1 of 2 pancreatic surgeons (RBA or TWB). Following surgery, all patients were referred to medical oncology for consideration of adjuvant chemotherapy or investigational protocols.

Histologic Evaluation

Standardized pathologic examination of surgical specimens was performed and the pathologic stage determined according to *AJCC Cancer Staging Manual* (6th edition) guidelines.[12] A pathologist specializing in pancreatobiliary

Borderline Resectable Subtypes

A Abutment of SMA/celiac axis ≤ 180°
Abutment or encasement (> 180°) of short segment of hepatic artery
Short-segment occlusion of SMV, PV, SMV-PV confluence amenable to resection & reconstruction

B Concern for possible extrapancreatic metastatic disease
Known N1 disease

C Marginal performance status (Zubrod 3)
Severe preexisting comorbidities requiring extensive evaluation or treatment prior to operation

FIG. 2 Subtype classification of patients with borderline resectable pancreatic adenocarcinoma. SMA, superior mesenteric artery; SMV, superior mesenteric vein; PV, portal vein

pathology graded the histologic tumor response using previously published grading criteria: grade I response was demonstrated ≥90% remaining viable tumor, grade IIa had 50–89% viable tumor remaining, grade IIb was equivalent to 10–49% viable tumor, grade III tumors had 1–9% remaining viable tumor, and Grade IV had no remaining viable tumor.[13]

Statistical Analysis

Data regarding time to recurrence and time to last follow-up were calculated from the date of diagnosis. Data were analyzed using the GraphPad Prism software (GraphPad Prism version 5, GraphPad Software, La Jolla, CA). Categorical variables were compared using the chi-square test. Contiguous variables were analyzed using a 2-tailed, unpaired *t* test with Welch correction. Survival curves were generated by the Kaplan–Meier method and compared using the log-rank test.[14] *P* values of ≤ .05 were considered to be statistically significant.

RESULTS

Between August 2005 and August 2008, 170 patients were evaluated at our Surgical Oncology clinics with a diagnosis of PDA. Following clinical evaluation and radiologic staging, 75 patients (44%) were classified as having potentially resectable tumors, 55 patients (32%) had unresectable tumors, and 40 (24%) were determined to have borderline resectable tumors. Demographics and preoperative characteristics for patients with borderline resectable disease are listed in Table 1. The median age was 66 years (range 45–83), and nearly two-thirds (63%) were male. The pancreatic head was the most common site of occurrence (90%) with 5% of lesions occurring each in the body and tail of the gland. Also, 30 patients (75%) with a borderline resectable tumor were further classified as subtype A, 5 (12.5%) as subtype B, and 5 (12.5%) as subtype C.

TABLE 1 Demographics and preoperative characteristics of 40 patients with borderline resectable pancreatic ductal adenocarcinoma

Age, years	
Median (mean)	66 (67)
Range	45–83
Gender	
Male	25 (63%)
Female	15 (37%)
Tumor location	
Head	36 (90%)
Body	2 (5%)
Tail	2 (5%)
MDACC BR Classification	
A	30 (74%)
B	5 (13%)
C	5 (13%)
Pretreatment CA19-9, U/mL	
Median (mean)	228 (1346)
Range	<1–13,013
Tumor size, cm	
Median	3.5
Range	1.5–6.5

MDACC MD Anderson Cancer Center, *BR* borderline resectable

A summary of the treatment of all 170 patients is outlined in Fig. 1b. There were 75 patients classified as potentially resectable and 51 of these patients (68%) underwent surgical resection, while the remaining 24 (32%) had occult metastatic disease discovered at laparotomy. Each of the 40 patients with borderline resectable tumors began neoadjuvant treatment. Of these patients, 6 (15%) were not restaged: 3 were lost to follow-up, 1 discontinued treatment secondary to intolerance, and 2 had not completed treatment at the time of this study. Of the 34 patients who completed neoadjuvant therapy, 12 (35%) were restaged with MRI and classified as unresectable. Of these, 3 patients (25%) had developed distant metastases (lung and liver) while the other 9 (75%) experienced local progression of their primary tumor, e.g., further encasement of the SMA.

Of 34 patients who completed neoadjuvant therapy, 22 (65%) demonstrated a lack of progression and were consented for surgery. Pancreatectomy was not completed in 6 patients (27%) due to locally advanced disease ($n = 1$) or occult distant metastases ($n = 5$) found at laparotomy. Also, 16 patients (64%) underwent pancreatic resection. Demographics, tumor profiles, and surgical data of the patients completing surgery are listed in Table 2. The

TABLE 2 Clinical, pathologic, and perioperative characteristics of 16 patients with borderline resectable pancreatic cancer who underwent pancreatectomy

	All patients	A	B	C	*P* value
N	16	12 (75%)	1 (6%)	3 (19%)	
Age, years					
Median	65	64	64	67	.810
(Range)	(45–83)		(45–83)	(64)	(57–71)
Time to surgery, weeks					
Median	19	19	32	19	.102
(Range)	(12–41)	(12–41)	(32)	(19–23)	
Operative time, minutes					
Median	585	615	780	510	.055
(Range)	(270–780)	(270–720)	(780)	(420–540)	
Estimated blood loss, cc					
Mean	500	550	1000	350	.858
(Range)	(100–2400)	(100–2400)	(1000)	(150–400)	
Vascular resection	4 (25%)	4 (33%)	0 (0%)	0 (0%)	.411
Length of stay, days					
Median	8	8	22	8	.092
(Range)	(5–32)	(5–32)	(22)	(6–11)	
Tumor size, cm					
Median (mean)	3.8 (3.7)	3.7 (3.8)	3 (3)	4 (3.7)	.748
Range	1.5–6.5	1.5–6.5	3	2.3–4.7	
Treatment response					
I	3 (19%)	2 (17%)	1 (100%)	0 (0%)	.101
IIa	5 (31%)	5 (31%)	0 (0%)	0 (0%)	.298
IIb	2 (13%)	1 (6%)	0 (0%)	1 (33%)	.467
III	6 (37%)	4 (33%)	0 (0%)	2 (67%)	.411
IV	0 (0%)				
Margin status					
R0	14 (88%)	10 (83%)	1 (100%)	3 (100%)	.298
R1	2 (12%)	2 (17%)	0 (0%)	0 (0%)	
Perineural invasion	8 (50%)	7 (58%)	0 (0%)	1 (33%)	.435
Lymph node status					
No. of patients with positive nodes	3 (19%)	3 (25%)	0 (0%)	0 (0%)	.540
No. of nodes examined, median (mean)	10 (11)	11 (12)	9 (9)	9 (7)	.449
No. of nodes examined, range	2–22	2–22	9	4–9	

median time from diagnosis to surgery in these 16 patients was 19 weeks (range 12–41), and there were no significant differences in this time among the different subtypes. Pancreaticoduodenectomy was performed in 13 of the 16 patients, while 2 patients underwent total pancreatectomy, and 1 had a distal pancreatectomy. The median operative time was 585 min (range 270–780), with a median estimated blood loss of 500 mL (range 100–2400 mL). Vascular resections (all for SMV/PV invasion) were performed in 4 patients (25%), all with subtype A borderline resectable tumor. The median length of stay was 8 days (range 5–32). There was no significant difference between the different borderline resectable subtypes with respect to the above variables. There were 6 patients (38%) who experienced 1 or more postoperative complications including *Clostridium difficile* colitis ($n = 3$), myocardial infarction ($n = 1$), intra-abdominal hemorrhage ($n = 1$), and a superficial wound infection ($n = 1$). One perioperative death occurred in a patient who succumbed to respiratory failure resulting from pulmonary embolism complicated by pneumonia.

Of the 40 patients classified as borderline resectable, 18 patients were treated with our accelerated chemoradiation protocol. Of these patients, 8 (44%) went on to resection. The remaining 22 patients were treated with conventional chemoradiation and 8 (36%) went onto surgery. None of

the patients completing the accelerated fractionation protocol experienced a grade IV toxicity, and only 1 patient (13%) experienced a grade III toxicity (nausea). Grade I fatigue was the most common toxicity (75%), followed by grade I nausea (63%). No patient required hospitalization or experienced hematologic toxicity.

Pathologic specimens were available for the 16 patients who underwent pancreatic resection. The median tumor size was 3.8 cm (range 1.5–6.5 cm, Table 2). Microscopically positive margins were present in 2 patients (17%), one at the SMA margin and the other at the cut edge of the common hepatic artery. Both patients had subtype A tumors. Perineural invasion was observed in 7 of 12 patients with subtype A tumors and in 1 of 3 with a subtype C tumors. A treatment response of greater than 10% (grades II–IV) was observed in 13 patients (81%), with 6 patients (38%) demonstrating >90% response (<10% viable tumor remaining; grade III). A complete pathologic response (grade IV) was not observed in any patient. Of the 8 patients who were treated with the accelerated protocol, 5 (63%) demonstrated a >90% treatment effect, compared with 1 of 8 patients (13%) treated with conventional schedules ($P < .05$). There were no significant differences in treatment response observed among the different tumor subtypes. A median of 10 lymph nodes (range 2–22) was recovered from each specimen. Lymph node metastases were detected in 3 of the 16 patients (19%); 2 patients had 1 positive node each, while the 3rd had microscopic tumor in 9 of 15 nodes.

Of the 16 patients undergoing resection, 14 (88%) received adjuvant gemcitabine therapy. The 2 patients not receiving adjuvant chemotherapy died prior to the initiation of therapy. At the time of last follow-up, 10 of the 40 patients (25%) classified as having borderline resectable tumors were alive with a median follow-up time of 13 months (range 2–31 months) and a median overall survival of 12 months. Of the 16 patients who underwent resection, 3 (19%) developed tumor recurrences at a median of 12 months (range 9–18 months); 2 of these patients have died. Of the remaining 13 patients, 2 had R1 resections and have since died, 1 patient died secondary to respiratory failure following surgery, 1 died secondary to cardiac causes, and 3 others have been lost to follow-up. Of the 16 patients who had surgery 7 (44%) remain alive with a median survival of 23 months compared with 3 of the 24 patients (13%) with borderline resectable tumors who did not undergo pancreatectomy ($P = .0002$, Fig. 3a) and 16 of 47 patients (34%) with potentially resectable cancer who underwent pancreatectomy (median survival 20 months, range 2–43 months; $P = .67$, Fig. 3b). Patients undergoing accelerated chemoradiation demonstrated a trend toward increased survival compared with patients receiving conventional neoadjuvant schedules ($P = .195$, Fig. 3c).

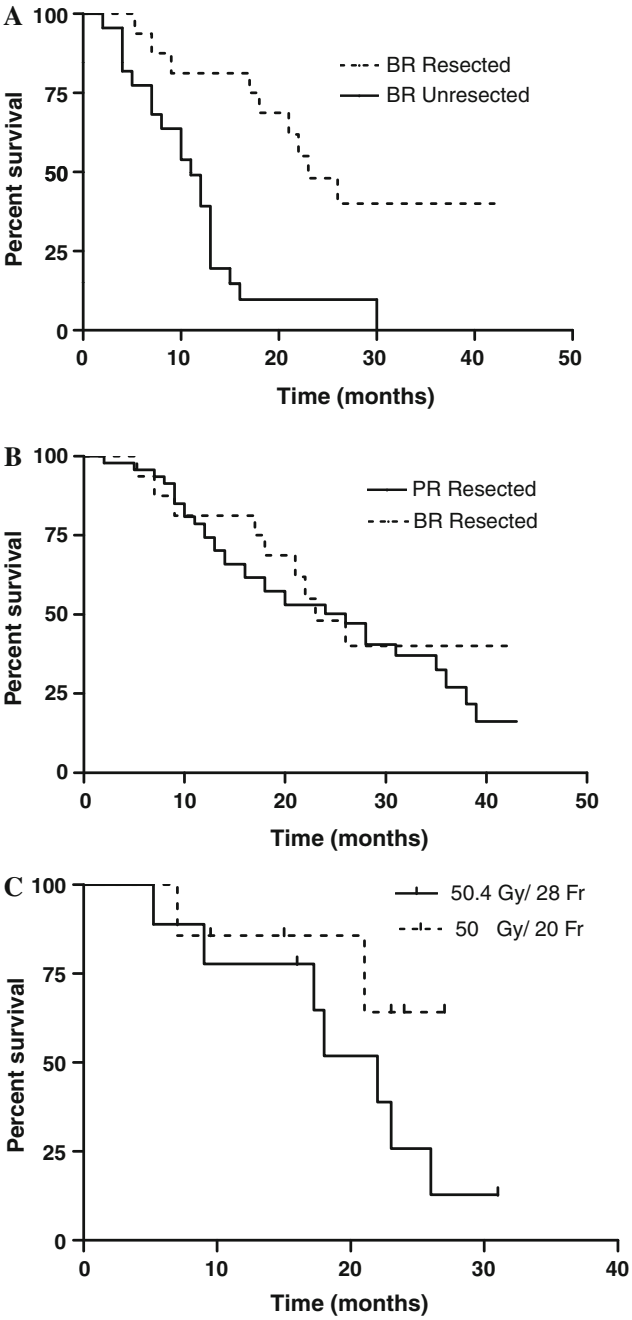

FIG. 3 Kaplan-Meier survival curves for patients with potentially resectable and borderline resectable PDA. **a** Curves comparing resection (solid) versus no resection (broken) in borderline resectable patients. **b** Curves comparing resected borderline resectable patients (solid) versus potentially resectable PDA who underwent resection (broken). **c** Curves comparing standard fractionation chemoradiation (solid) versus accelerated fractionation chemoradiation (broken)

DISCUSSION

Since patients with borderline resectable PDA are at high risk for a margin-positive resection and poor survival secondary to local recurrence, poor performance status, and

uncertainty regarding the presence of metastatic disease, they may benefit from neoadjuvant therapy. No standardized approach to borderline resectable patients currently exists. In this report, we describe the outcomes of patients with borderline resectable PDA after treatment with neoadjuvant capecitabine-based chemoradiation.

Borderline resectable PDA represents unfavorable tumor biology, and expectations following therapy should be formulated accordingly. The use of neoadjuvant therapy in patients with borderline resectable PDA allows selection of patients with the most favorable biology and those who are mostly likely to benefit from surgery. We have identified 40 patients with borderline resectable PDA, of whom 22 (55%) completed neoadjuvant chemoradiation therapy and demonstrated lack of progression of disease on restaging imaging. Of these, 16 patients (40%) went on to resection and the remaining 6 (15%) had occult metastatic disease discovered at exploration. Similar percentages of borderline resectable patients completing all therapy, including surgery, have been reported by the MDACC group (41%) and in an independent phase I trial (33%).[10,15]

Numerous reports have demonstrated an R0 resection as the most important determinant of overall survival in patients with PDA, illustrating the importance of accurate preoperative staging.[4–8,16,17] The use of neoadjuvant therapy in patients with locally advanced pancreatic cancer appears to provide a higher rate of R0 resections (85–94%) compared with patients treated with surgery alone.[11,18–20] In our study, 88% of patients with borderline resectable tumors underwent an R0 resection, despite most of these patients having SMA abutment on preoperative imaging. Not surprisingly, the 2 patients with positive arterial margins each had locally invasive disease preoperatively (MDACC subtype A), while none of the subtype B or C patients had an R1 resection.

Standardized preoperative therapy strategies have not been established for borderline resectable PDA. Numerous trials (Table 3) have evaluated the use of radiosensitizing agents, cytopathic agents, or targeted therapies with concurrent radiotherapy in patients with potentially resectable, locally advanced, or borderline resectable disease resulting in 5–74% of patients undergoing a margin-negative resection.[13,21–29] Often these trials have used multiagent therapy with prolonged schedules. Our institution employs an accelerated schedule of 50 Gy of EBR in 20 fractions, compared with the conventional schedule of 50.4 Gy in 28 fractions. Patients undergoing neoadjuvant therapy outside of our institution received 50.4 Gy in 28 fractions. Patients receiving our accelerated protocol were significantly more likely to demonstrate a grade III treatment effect compared with patients who underwent conventional schedules (63% vs 13%, $P < .05$). This profound tumor response has not been demonstrated in previous studies using other treatment strategies. For example, in the MDACC series 18% of the 66 resected patients had a grade III/IV response, which was similar to the patients treated with conventional fractionation in our study.[10] Interestingly, the profound treatment effect with accelerated fractionation radiation translated into significantly longer survival (Fig. 3c). Similarly, Katz et al. also observed that treatment effect was associated with overall survival.[10] However, the small number of patients in our study limits conclusions regarding the effect of our treatment regimen on survival.

Overall, this is a well-tolerated neoadjuvant treatment protocol. None of the patients in our protocol experienced grade IV toxicity or required hospitalization, while 1 (13%)

TABLE 3 Comparison of chemoradiation regimens for patients with pancreatic cancer

Author	*N*	PR/LA	Regiment	Dose (Gy)	No. fractions/ weeks	No. patients resected	Median survival (months)	Toxicity (>grade 3)
Pisters (2002)	35	PR	XRT, paclitaxel	30	10/2	20 (57%)	19	16 (46%)
Talamonti (2006)	20	PR	XRT, Gem	36	15/3	17 (85%)	26	1 (5%)
Snady (2000)	68	LA	XRT, 5-FU, cisplatin, streptozocin	54	27/8	20 (29%)	32.3	19 (27%)
Crane (2001)	51	LA	XRT, Gem	33	11/2	6 (12%)	[a]	17 (33%)
Aristu (2003)	47	LA	XRT, 5-FU, cisplatin, paclitaxel or Gem or docetaxel	45	25/5	9 (19%)	23	29 (59%)
Joensuu (2004)	28	LA	XRT, Gem	50.4	28/5	20 (71%)	25	23 (74%)
Pipas (2005)	24	LA	XRT, Gem, docetaxel	50.4	26/5	13 (54%)	14	8 (33%)
Katz (2008)	160	BR	XRT, 5-FU, paclitaxel, or Gem	50.4 or 30	28/6 or 10/2	66 (41%)	27	25 (20%)
Current Study	40	BR	XRT, chronomodulated capecitabine	50.4	20/4 or 28/6	16 (40%)	23	1 (13%)

BR borderline resectable, *PR* potentially resectable, *LA* locally advanced, *XRT* external beam radiation, *Gem* gemcitabine, *5-FU* 5-Flourouracil

[a] Data not reported

had a grade III toxicity. Previous studies of neoadjuvant chemoradiation have shown toxicity rates of 20–74%.[10,25,30–34] Thus, the higher doses of radiation given per each fraction do not appear to increase the severity of toxicity.

Limitations of our study include its retrospective design, small sample size, and limited follow-up. Although our analysis was performed as a retrospective review, patients with PDA are stratified at our multidisciplinary conference in a prospective fashion, and data considered for analysis were collected in a prospective manner. Except for the large series reported by the MDACC group, our relatively small sample size (40 borderline resectable patients) is consistent with other studies reporting cohorts of 13, 18, and 66 patients.[10,11,15] Additional larger, multi-institutional trials are needed to further validate outcomes after neoadjuvant therapy for borderline resectable PDA. The relatively recent introduction of a standardized borderline resectable classification scheme precludes long-term follow-up, consistent with our relatively short follow-up of a median of 20 months. Extended follow-up of these patients is required to determine the long-term benefits of this therapy. With our current protocol, it is certainly possible that some patients with occult metastatic disease were treated with neoadjuvant chemoradiation and the associated risks and toxicities. Although not implemented in our current practice, it may be rational to consider performing exploratory laparoscopy in borderline resectable patients prior to initiating any chemoradiation protocols to rule out metastatic disease.

In summary, we present a protocol of chronomodulated capecitabine-based accelerated chemoradiation for patients with borderline resectable PDA. Neoadjuvant capecitabine-based chemoradiation appears to improve resectability and survival in patients with borderline resectable PDA, and our results are similar to previous reports in which patients received protracted courses of additional neoadjuvant chemotherapy. Additionally, our data with chronomodulated capecitabine-based accelerated chemoradiation suggests an improvement in treatment effect over more conventional regimens. Further prospective evaluation of these findings associated with accelerated chronomodulated chemoradiation and the treatment of this high-risk subset of patients with PDA is warranted.

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