Original Article

A Multi-Institutional Phase 2 Study of Neoadjuvant Gemcitabine and Oxaliplatin With Radiation Therapy in Patients With Pancreatic Cancer

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BACKGROUND: The purpose of this study was to evaluate preoperative treatment with full-dose gemcitabine, oxaliplatin, and radiation therapy (RT) in patients with localized pancreatic cancer. **METHODS:** Eligibility included confirmation of adenocarcinoma, resectable or borderline resectable disease, a performance status ≤ 2, and adequate organ function. Treatment consisted of two 28-day cycles of gemcitabine (1 g/m^2 over 30 minutes on days 1, 8, and 15) and oxaliplatin (85 mg/m^2 on days 1 and 15) with RT during cycle 1 (30 Gray [Gy] in 2-Gy fractions). Patients were evaluated for surgery after cycle 2. Patients who underwent resection received 2 cycles of adjuvant chemotherapy. **RESULTS:** Sixty-eight evaluable patients received treatment at 4 centers. By central radiology review, 23 patients had resectable disease, 39 patients had borderline resectable disease, and 6 patients had unresectable disease. Sixty-six patients (97%) completed cycle 1 with RT, and 61 patients (90%) completed cycle 2. Grade ≥ 3 adverse events during preoperative therapy included neutropenia (32%), thrombocytopenia (25%), and biliary obstruction/cholangitis (14%). Forty-three patients underwent resection (63%), and complete (R0) resection was achieved in 36 of those 43 patients (84%). The median overall survival was 18.2 months (95% confidence interval, 13-26.9 months) for all patients, 27.1 months (95% confidence interval, 21.2-47.1 months) for those who underwent resection, and 10.9 months (95% confidence interval, 6.1-12.6 months) for those who did not undergo resection. A decrease in CA 19-9 level after neoadjuvant therapy was associated with R0 resection ($P = .02$), which resulted in a median survival of 34.6 months (95% confidence interval, 20.3-47.1 months). Fourteen patients (21%) are alive and disease free at a median follow-up of 31.4 months (range, 24-47.6 months). **CONCLUSIONS:** Preoperative therapy with full-dose gemcitabine, oxaliplatin, and RT was feasible and resulted in a high percentage of R0 resections. The current results are particularly encouraging, because the majority of patients had borderline resectable disease. *Cancer* 2013;119:2692-700. © *2013 American Cancer Society*.

KEYWORDS: pancreatic cancer; neoadjuvant; gemcitabine; oxaliplatin.

INTRODUCTION

Pancreatic carcinoma is associated with a poor prognosis in all stages.[1] In patients who present with resectable disease, surgery offers the potential for a cure, and postoperative therapy provides benefit.[1-4] Unfortunately, the majority of patients with localized pancreatic cancer present with borderline resectable or unresectable disease, and initial surgical therapy is unlikely to result in a complete (R0) resection.[1,5,6]

In contrast to surgery first, preoperative therapy offers advantages for patients who have localized pancreatic cancer. Patients can receive systemic therapy sooner, generally with better tolerance and compliance. Preoperative treatment

appears to increase the rate of margin negative resections in borderline lesions.[7,8] Furthermore, recognition of metastatic disease during preoperative therapy spares patients major surgery. Finally, isolated local progression during preoperative therapy, precluding resection, appears to be uncommon, as reported in 2 sequential studies involving 176 patients.[9,10]

We previously conducted a phase 1 study of oxaliplatin added to full-dose gemcitabine and radiation in patients with pancreas cancer.[11] This approach is intended to maximize systemic therapy while simultaneously enhancing the effects of radiation.[12-15] On the basis of safety and encouraging results in patients with resectable disease, here, we report a multi-institution phase 2 study of neoadjuvant chemoradiotherapy, surgery, and adjuvant chemotherapy in patients with resectable and borderline resectable pancreatic cancer.

MATERIALS AND METHODS

Patients who had pathologically confirmed pancreatic carcinoma and localized disease were eligible for this study. Resectability was assessed by multidetector (computed tomography [CT]) scan using a multiphase, contrast-enhanced technique and applying 2008 National Comprehensive Cancer Center Network criteria (version 1). Briefly, tumors were designated as resectable with a clear fat plane around the celiac and superior mesenteric arteries and patent superior mesenteric and portal veins. Patients were deemed borderline resectable if they had severe unilateral superior mesenteric vein or portal vein impingement, tumor abutment of the superior mesenteric artery, gastroduodenal artery encasement up to the origin from the hepatic artery, or colon invasion. Further eligibility criteria included a life expectancy >12 weeks; a Zubrod performance status ≤2; and adequate hematologic, renal, and hepatic function. Patients with grade ≥2 neuropathy, those who had received prior therapy for pancreatic cancer, and those who had received prior abdominal radiation were not eligible. The institutional review board of each participating institution approved the trial. Written informed consent was obtained from all patients before treatment initiation. This clinical trial is registered with clinicaltrials.gov (registration no. NCT00456599).

Treatment

Protocol treatment consisted of four 28-day cycles of chemotherapy: 2 cycles before surgery and 2 cycles after. Gemcitabine (1 g/m^2 infused over 30 minutes) was administered on days 1, 8, and 15 of each cycle; oxaliplatin (85 mg/m^2 infused over 90 minutes) was administered on days 1 and 15. Radiation therapy was delivered concurrently with the first cycle of chemotherapy in 2-Gray [Gy] fractions (total dose, 30 Gy). Three-dimensional planning was used, limiting the target volumes to gross disease with a 1-cm margin and allowing no elective lymph node irradiation, as described previously.[11] Treatment plans were reviewed and approved by a central radiation oncologist (E.B.-J.) before the initiation of treatment.

Patients were evaluated after the second cycle of chemotherapy; and, if they had no evidence of metastasis or local progression that precluded resection, then surgery was offered 2 to 4 weeks after the last chemotherapy cycle. After resection, patients received adjuvant chemotherapy, which resumed within 12 weeks of surgery.

Adjustments to chemotherapy doses were based on the toxicity experienced during previous therapy and on the platelet and absolute neutrophil (ANC) counts on the day of treatment. For an ANC ≥1000/mm^3 and platelets ≥75,000/mm^3, patients received full doses. For an ANC >500/mm^3 and <1000/mm^3 and/or platelets >50,000/mm^3 and <75,000/mm^3, patients received a 50% reduction in the gemcitabine dose and a 25% reduction in the oxaliplatin dose. For an ANC ≤500/mm^3 or platelets ≤50,000/mm^3, chemotherapy was held until the patient recovered to an ANC ≥1000/mm^3 and a platelet count ≥75,000/mm^3. Both agents were held for any nonhematologic toxicities grade ≥3, and treatment resumed upon improvement to grade ≤2. If chemotherapy was held, then, when resumed, doses of both agents were reduced by 25%. If a hold occurred during cycle 1, then radiation treatment also was held. Beyond cycle 1, if chemotherapy was held, then that treatment day was dropped. If toxicity and recovery were not sufficient to allow treatment resumption within 3 weeks, then patients were taken off protocol.

Assessment of Response and Surgical Therapy

Interpretation of baseline CT scans and imaging studies after preoperative therapy and decision making regarding surgery were undertaken at the institutional level. A blinded post hoc central review of baseline and presurgical CT scans was performed upon completion of the study by a single radiologist (I.R.F.). For this report, that central review determined resectability status and response after neoadjuvant therapy according to Response Evaluation Criteria in Solid Tumors (RECIST).[16]

For all patients who underwent surgery, the details collected included the type and duration of surgery,

vascular resection and/or reconstruction; the estimated blood loss; the length of hospitalization; and data on readmission or reoperation within 30 days. A blinded central pathology review of all resection specimens was performed by a single pathologist (J.K.G.) and included assessment of tumor size, grade, margin status, lymph node number and involvement, and histologic evaluation of response to treatment.[17] Quality-of-life measurements were assessed before, during, and after therapy and will be subject of a separate report.

Statistical Analysis

This trial was designed to demonstrate an improvement in 2 year disease-free survival (DFS). We hypothesized that the treatment regimen would increase DFS by at least 15 percentage points based on an estimate of 35% derived from resected patients who received postoperative adjuvant gemcitabine on the CONKO-001 trial.[3] For the current trial, 68 patients were required to provide 80% statistical power using a 1-sided test. Secondary endpoints included the rate of successful resection and survival. When designing the trial, we assumed that approximately 70% of those enrolled would be resectable at entry and that most would undergo successful resection (R0). However, the proportion of accrued patients who had borderline resectable disease was significantly higher than anticipated (approximately 70% vs 30%). The trial continued with additional emphasis placed on determining the rate of R0 resection and clinical outcomes in the study population.

The ability to achieve an R0 resection and tumor response (complete plus partial responses) was tested for significant associations with patient, tumor, and treatment characteristics using chi-square and t test statistics for categorical and continuous data, respectively. The characteristics considered were patient age at study entry, race, sex, performance status, baseline overall quality of life, baseline assessment of resectability, the presence of vessel contact (none, artery, and/or vein), tumor site in the pancreas (head, body, or tail), tumor size before and after neoadjuvant treatment and RECIST response, the pretreatment carbohydrate antigen 19-9 (CA 19-9) level (a serum tumor marker; also called sialylated Lewis a antigen) and change after therapy, and histologic response to neoadjuvant treatment. Clinical outcome was defined as overall survival (OS) and DFS. The times to events were calculated from the first day of treatment to the date of death (OS) or the date of progression or death (DFS). Patients who did not experience the events of interest were censored on their last contact date. Time-to-event endpoints were summarized using the product-limit method

TABLE 1. Patient Demographics and Disease Characteristics

Characteristic	No. of Patients (%)
Total no. of patients	68
Treatment center	
University of Michigan	29 (43)
Johns Hopkins University	16 (23)
Ohio State University	13 (19)
Princess Margaret Hospital	10 (15)
Age: Median [range], y	64 (42-83)
Sex	
Men	32 (47)
Women	36 (53)
Zubrod performance status	
0	40 (59)
1	26 (38)
2	2 (3)
Tumor size: Median [range], cm	3.1 [1.4-7.8]
Site of lesion	
Head	45 (66)
Body	18 (27)
Tail	5 (7)
Tumor classification: Central radiology review	
T1/T2	8 (12)
T3	56 (82)
T4	4 (6)
Resectability: Central radiology review	
Resectable	23 (34)
No vessel contact	13
PV/SMV contact	10
Borderline resectable	39 (57)
PV/SMV impingement, not arterial	22
SMA abutment	14[a]
Other, contiguous organ involvement	3
Unresectable	6 (9)
PV/SMV encasement/occlusion	2
SMA encasement	3
Celiac artery contact	1
Baseline CA 19-9: Median [range], U/mL	175 [ND to 10,776]

Abbreviations: ND, not determined; PV, portal vein; SMV, superior mesenteric vein; SMA, superior mesenteric artery.
[a] Eleven patients who had SMA abutment also had venous contact.

of Kaplan and Meier. A best multivariable model to explain OS was constructed using the proportional hazards model, simultaneously modeling the covariates that were associated significantly with survival in univariate analysis. The best model was chosen by iteratively removing nonsignificant covariates until only significant ($P < .05$) covariates remained. P values $\leq .05$ were considered significant for all test statistics.

RESULTS

Patient and Primary Tumor Characteristics

Seventy-five patients were consented and registered on the study between July 2007 and February 2010. One patient was ineligible because of a diagnosis of neuroendocrine cancer, and 3 patients who did not receive any study treatment were not considered in further analyses. Seventy-one eligible patients were evaluable for safety. Of these, 1
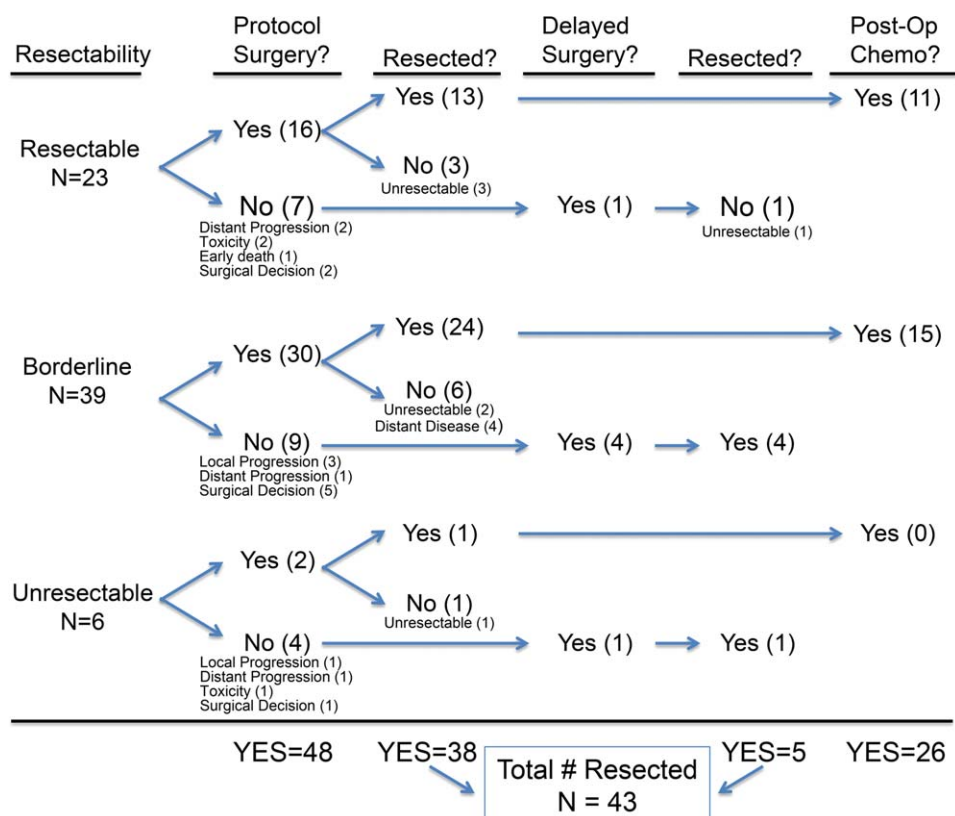
Figure 1. This is a flow chart of the evaluable patients grouped by resection status and detailing treatment received. Surgical decision indicates delayed operation for additional off-protocol chemotherapy to increase the likelihood of resection (see text).

patient was removed from study during cycle 1 for non-compliance, and 2 additional patients withdrew for reasons not related to toxicity or progression. The final evaluable population included 68 patients (Table 1).

Treatment

Sixty-six patients (97%) completed cycle 1 of chemotherapy and radiation (30 Gy), with 19 patients (29%) requiring a delay (generally 1 week). Sixty-one patients (90%) initiated a second cycle of chemotherapy. After cycle 2, 4 patients were judged inoperable because of medical conditions, and 8 patients progressed (12%) either locally (n = 4) or distantly (n = 4), precluding resection (Fig. 1). Eight additional patients were removed from protocol to continue chemotherapy as opposed to proceeding to surgery. Six of those patients subsequently underwent surgical exploration, as described below.

Forty-eight patients (71%) underwent laparotomy according to the protocol (and 6 additional patients underwent delayed surgery). In total, 43 patients underwent resection (including 5 off protocol), leading to a resection rate of 63% of treated, evaluable patients and 80% of patients who

underwent surgical exploration. After resection, 26 patients (68%) initiated adjuvant therapy, and 24 (63%) completed a fourth cycle of chemotherapy.

Response

Comparing pretreatment versus post-treatment imaging (Table 2), 5 patients (7%) had a partial response, and 50 patients (74%) demonstrated stable disease, including 19 (28%) who had a minor response (10%-29% decrease in tumor longest diameter). Twelve patients had RECIST progression (18%) with a $\geq 20\%$ increase in tumor longest diameter (n = 9) or metastatic disease (n = 3). Notably, 5 of 9 patients who had progression according to RECIST underwent R0 resection without additional therapy. CA 19-9 levels that were available both pretreatment and post-treatment and were considered informative (>40 U/mL at least once; n = 50) decreased in 74% of patients.

Surgical Parameters

Thirty-two patients underwent standard pancreaticoduodenectomy, 11 patients underwent distal-subtotal pancreatectomy; of these 17 patients (40%) had vascular

TABLE 2. Response to Preoperative Therapy

Response	No. of Patients (%)
Radiographic, n = 67	
PR	5 (7)
SD	50 (74)
PD	12 (18)
CA 19-9	
Elevated ≥40 U/mL before or after treatment	50
Decreased	37 (74)
Increased	13 (26)
Surgical pathology	
No. of centrally reviewed cases	43 (100)
Tumor size: Median [range]	3 [0.3-5.3]
Tumor classification	
T1/T2	11 (26)
T3	31 (72)
T4	1 (2)
Tumor grade	
1	3 (7)
2	32 (74)
3	8 (19)
Positive lymph node status, N1	21 (49)
No. of lymph nodes resected: Median [range]	14 [1-28]
Margin resection status	
R0	36 (84)
R1	5 (12)
R2	2 (5)
Response grade of tumor cell destruction	
0%-50%	19 (44)
51%-90%	15 (35)
>90%	9 (21)

Abbreviations: PR, partial response; PD, progressive disease; SD, stable disease.

TABLE 3. Safety

	No. of Patients (%)			
	Neoadjuvant Therapy, n = 71		Adjuvant Therapy, n = 38	
Toxicity	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic				
Any	26 (37)	13 (18)	11 (29)	8 (21)
Leukopenia	22 (31)	2 (3)	9 (24)	3 (8)
Lymphopenia	12 (17)	4 (6)	3 (8)	
Neutropenia	17 (24)	6 (8)	7 (18)	7 (18)
Anemia	6 (8)			
Thrombocytopenia	14 (20)	4 (6)	5 (13)	1 (3)
Nonhematologic				
Any	33 (46)	1 (1)	4 (11)	
Biliary obstruction				
Cholangitis	8 (11)			
No cholangitis	2 (3)			
Transaminitis	13 (18)		1 (3)	
Dehydration	5 (7)			
Fatigue	4 (6)			
Nausea and vomiting	4 (6)			
Hyperglycemia	5 (7)			
Hypokalemia	4 (6)			
Pain	3 (4)			
Chest pain	1 (1)			
Hypotension	1 (1)			
Anorexia	1 (1)			
Ascites	1 (1)			
Enteritis	1 (1)			
Hypoalbuminemia	1 (1)			
Increased creatinine phosphokinase		1 (1)		
Perforated bowel	1 (1)			
Rash	1 (1)			
Syncope	1 (1)			
Thrombosis	1 (1)			
Neuropathy			1 (3)	
Weight loss			1(3)	
Thrombotic microangiopathy			1 (3)	

resection and/or reconstruction. The mean operative time was 7.5 hours (range, 2-14 hours), and the mean estimated blood loss was 1010 mL (range, 100-4000 mL). The median duration of hospitalization was 8 days (range, 3-20 days), and 6 patients (14%) were readmitted within 30 days. There was no 30-day perioperative mortality.

The surgical margins were free of microscopic disease in 36 patients(84%). Five patients underwent R1 resection, and 2 patients underwent R2 resection. Of 19 patients who had baseline superior mesenteric artery/celiac arterial contact, 13 patients underwent R0 resection, and 1 patient underwent R1 resection. Regional lymph nodes were involved in 21 of 43 resection specimens (49%). A treatment effect of at least 50% necrosis was noted in 24 patients (56%), and >90% tumor destruction was noted in 9 patients (21%).

Safety
Grade 3 and 4 toxicities experienced during preoperative therapy in 71 treated patients are summarized in Table 3. Nonhematologic toxicities that occurred in >10% of patients were limited to transaminitis 13 patients (18%) and biliary obstruction in 10 patients (14%), with associ-

ated cholangitis in 8 patients (11%). There were 2 deaths during the preoperative period, including 1 sudden death after cycle 1, which was believed cardiopulmonary (autopsy was declined), and a second patient who experienced progressive peritoneal cancer and infection after cycle 1. In total, 18 patients (25%) were hospitalized at least once during the preoperative period, and 4 patients were hospitalized more than once. Lower rates of grade 3 and 4 non-hematologic toxicities were observed with adjuvant therapy.

Patient Outcomes
At the last follow-up, 48 of 68 patients (71%) had died, including 23 of 25 patients (92%) who were not resected and 25 of 43 patients (58%) who underwent surgical resection. The median OS was 18.2 months (95% confidence interval [CI], 13-26.9 months) (Fig. 2a). For those
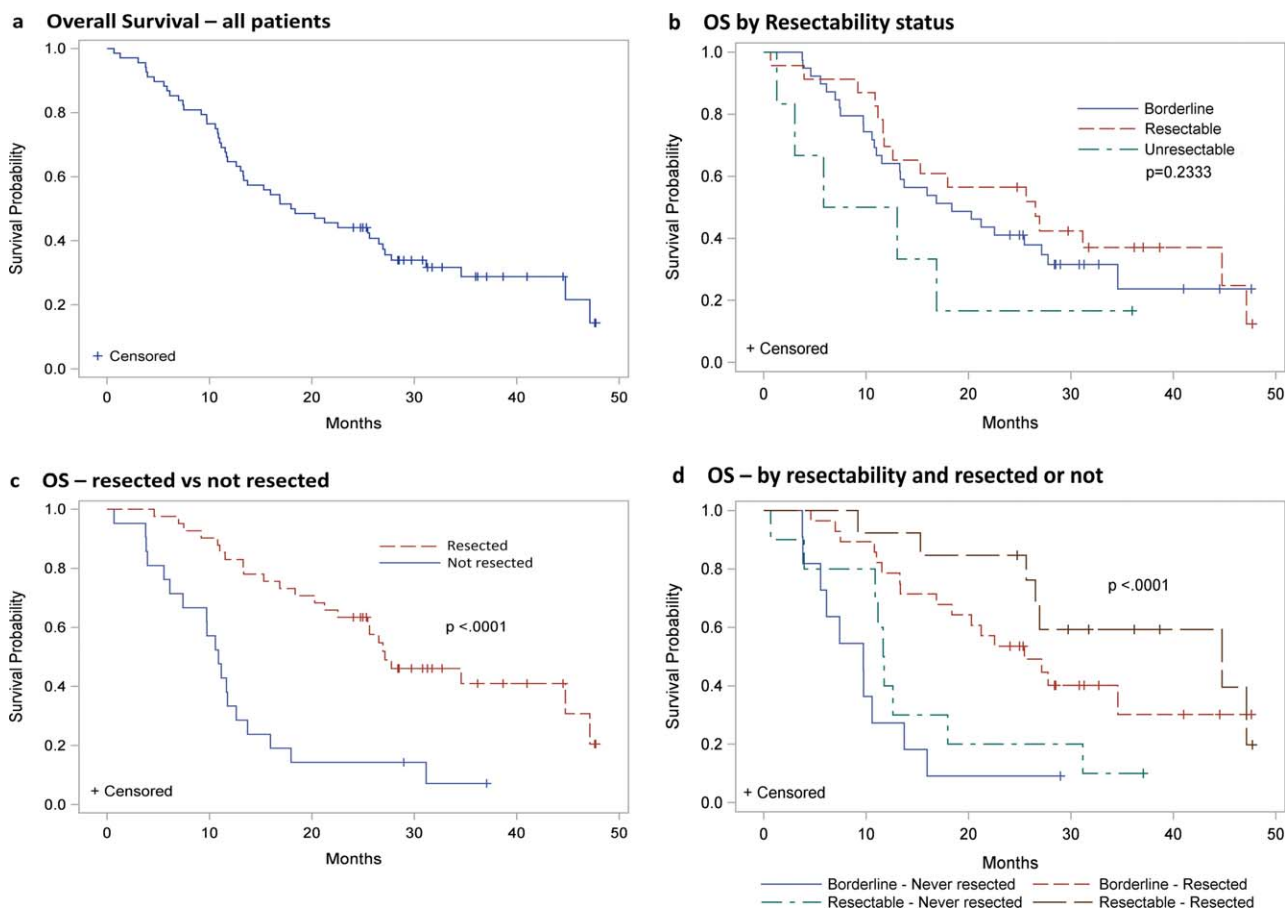
a Overall Survival – all patients

b OS by Resectability status

c OS – resected vs not resected

d OS – by resectability and resected or not

Figure 2. From the Kaplan-Meier survival analysis, estimated overall survival (OS) is illustrated for (a) all patients; (b) patients who had resectable, borderline resectable, or unresectable disease at baseline ($P = .2333$); (c) patients who either did or did not undergo resection ($P < .0001$); and (d) patients with who had either resectable or borderline resectable disease who either did or did not undergo resection ($P < .0001$).

patients who had resectable disease at presentation, the median survival was 26.5 months (95% CI, 11.8-44.7 months) compared with 18.4 months (95% CI, 11-27.1 months) for patients who had borderline resectable disease and 9.4 months (95% CI, 1.3 months to not evaluable) for those who had unresectable disease (Fig. 2b). Patients who underwent any resection had a median survival of 27.1 months (95% CI, 21.2-47.1 months) versus 10.9 months (95% CI, 6.1-12.6 months) for those who did not undergo resection (Fig. 2c). The median survival for patients who underwent R0 resection (n = 36) was 34.6 months (95% CI, 20.3-47.1 months). Finally, patients who presented with resectable status and underwent resection (n = 13) had a median survival of 44.7 months (95% CI, 25.6 months to not evaluated), and those who presented with borderline status and underwent resection (n = 28) had a median survival of 25.4 months (95% CI, 16.9 months to not evaluable) (Fig. 2d).

Of 41 patients who underwent R0/R1 resection, 22 patients developed recurrent disease at a median time after surgery of 10.4 months (range, 2.3-35.8 months). Recurrent disease was local only in 7 patients (17%), distant only in 10 patients (24%), and both local and distant in 5 patients (12%). Five additional patients died without documentation of their pattern of recurrence at a median time from surgery to death of 6.9 months (range, 1.8-10.1 months). The 2-year DFS estimate was 26.1% (95% CI, 16.1%-37.4%). Fourteen patients (21%) remained alive and disease-free at a median follow-up of 31.4 months (range, 24-47.6 months).

Patient, tumor, and response characteristics were evaluated for significant univariate associations with achieving R0 resection, survival time, and time to disease progression. None of the characteristics (listed above; see Statistical Analysis) were associated significantly with R0 resection with the exception of CA 19-9 response.

TABLE 4. Best Multivariable Model Explaining Overall Survival

Characteristic	HR	95% CI	P
Resection status			
No resection	5.4	2.8-10.6	< .001
R0	Reference		
R1/R2	1.2	0.4-3.2	.684
Sex			
Women	Reference		
Men	2.3	1.2-4.2	.009
Tumor site on pancreas			
Head	2.2	1.1-4.3	.024
Body/tail	Reference		

Abbreviations: CI, confidence interval; HR, hazard ratio.

Comparing any increase (n = 15) with a 0% to 50% decrease (n = 13) and a >50% decrease (n = 27) demonstrated that a decrease in CA 19-9 was associated with R0 resection (P = .02). Resection (R0 vs R1/R2 vs none), baseline quality of life, female gender, tumor in the pancreatic body or tail (compared with the pancreatic head), and lower CA 19-9 levels at baseline (continuous) were associated with improved survival (all P < .05). In the patients who underwent surgical resection (n = 43), longer surgery time (P = .03) and increased blood loss during surgery (P = .02) were associated with poorer survival, and marginal associations were observed with surgical procedure (Whipple was inferior to distal-subtotal pancreatectomy; P = .057) and histologic treatment effect (P = .068). None of the characteristics had an association with the time to progression.

The best multivariable model to explain OS in 68 evaluable patients from the covariates available is presented in Table 4. Incomplete resection (R1/R2) and the inability to undergo resection were associated significantly with reduced survival along with male gender and having a tumor located in the pancreatic head.

DISCUSSION

This multi-institutional trial is a continuation of a series of studies at the University of Michigan that have used full-dose gemcitabine with conformal radiation limited to gross tumor in patients with localized pancreatic cancer.[11,13,18-20] The central tenet of this approach is that standard (full) doses of chemotherapy will maximize systemic disease control while simultaneously sensitizing the primary tumor to concurrent radiation.[12-15] This is in contrast to other gemcitabine/radiation combinations in which patients receive gemcitabine at lower doses (weekly, 400-600 mg/m^2; biweekly, 40 mg/m^2) and radiation

includes clinically uninvolved lymph nodes.[9,10,21,22] In the current study, despite the addition of oxaliplatin at a standard dose, treatment was well tolerated with rates of hospitalization and nonhematologic grade 3 and 4 toxicities similar to, or lower than, previous studies.[9,10,19] Although the primary study endpoint of demonstrating an improvement in 2-year DFS was not achieved, principally because the majority of entered patients had borderline resectable disease, evidence of efficacy was noted. This therapy resulted in an R0 resection in 84% of patients who underwent surgery, with a resultant median survival of 34.6 months, which is notable in the context that 70% of resections were performed in borderline resectable (28 patients) or unresectable (2 patients) disease. Lymph nodes were involved in 49% of the resections, comparing favorably to a resectable patient population (72% in CONKO-001 and 66% in Radiation Therapy Oncology Group trial 97-04).[3,4] This result, along with the significant association of CA 19-9 response and R0 resection, suggests a treatment effect from preoperative therapy. For those patients who achieve any resection, a median survival of 27.1 months is similar to the median survival reported in the adjuvant phase 3 trials.[2-4] Appreciating that preoperative treatment is commonly offered to patients who have locally advanced disease, there is little prospective data for comparison with our trial, especially in patients who have borderline resectable disease.[19,23-25]

A persistent challenge to the development and evaluation of preoperative therapies for pancreatic cancer is accurate staging. Despite undergoing evaluations in academic medical centers with multidisciplinary pancreatic cancer programs, a post hoc central review of all CT scans in our study led to the recategorization of resectability status in a number of patients in both directions: 9 patients moved from borderline to resectable status, and 14 patients were upstaged, 8 from resectable to borderline status and 6 to unresectable status. This challenge of accurate staging is also reflected in changing definitions, which occurred during the conduct of this trial. The current definition of resectability is based on a consensus statement that was published in 2009.[26] Although we applied the 2008 definition throughout this report, using 2009 criteria to categorize our 68 evaluable patients, the number of resectable patients would decrease from 23 to 12, with 10 patients upstaged to borderline status and 1 patient moved to unresectable status.

The optimal time for surgery after neoadjuvant therapy is also difficult to define. The tumor may not regress on CT imaging despite clinical and CA 19-9

response.[27,28] Eight patients were removed from our protocol because of vascular involvement to receive additional chemotherapy before surgery, and 5 of those patients subsequently underwent R0 resection. The observation that others in the trial with an increase in tumor longest diameter ≥20% (n = 5) or with continuing contact on vessels after 2 cycles of treatment (n = 21) underwent R0 resections points to the difficulty in determining when surgery should be offered.

Several aspects of this report bear comment. The 2008 National Comprehensive Cancer Center Network resectability criteria used were inadequate; although they clearly defined resectable tumors, they did not easily distinguish between borderline and unresectable disease, especially for tumors outside the pancreatic head. The patient population was heterogeneous, and the likelihood of resectablilty at baseline varied by tumor location within the pancreas and by the presence and degree of contact with vein(s) and/or arteries. The treatment protocol was intended for resectable patients according to the study design/endpoints and the duration/intensity of preoperative therapy, yet eligibility criteria allowed us to accrue patients with more advanced disease. Finally, the utility of combination chemotherapy used here is uncertain. The regimen was based on meta-analyses that reported a survival benefit from gemcitabine-platin combinations in advanced disease, and it may be supported by recent data with the oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) combination.[29,30] Our study, however, was not designed to determine the contribution of oxaliplatin to gemcitabine-based treatment.

Weaknesses of the current study include difficulties in the accurate characterization of resectability, the entry of patients with unresectable disease, the removal of patients from protocol to continue chemotherapy before surgery, and the lower numbers of patients who received adjuvant treatment. Strengths of this study include the multi-institutional setting, the number of patients entered (especially those with borderline resectable pancreatic cancer), and the central review of imaging, radiation treatment plan, and pathology on resected specimens. This is one of the first prospective studies to establish what may be expected using the current definitions of resectability with regard to R0 resection rates and overall outcomes.

In summary, we report on a group of 68 patients with localized pancreatic cancer who, according to 2009 definitions, had resectable (n = 12), borderline resectable (n = 49), or unresectable (n = 7) pancreatic cancer.[26] After 2 cycles of preoperative chemotherapy with gemcitabine and oxaliplatin plus radiation during cycle 1, the majority of patients went on to undergo R0 surgical resection. The median survival for the entire population was 18.2 months, and, for those who achieved R0 resection, it was 34.6 months. On the basis of this experience, the study treatment can be recommended for patients with resectable or borderline resectable disease. For those who have more advanced disease, longer or more intensive chemotherapy and/or radiation therapy using higher doses should be further investigated.[31-33]

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CONFLICT OF INTEREST DISCLOSURES

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