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ORIGINAL ARTICLE – PANCREATIC TUMORS

Extended Neoadjuvant Chemotherapy for Borderline Resectable Pancreatic Cancer Demonstrates Promising Postoperative Outcomes and Survival

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ABSTRACT

Background. The optimum approach to neoadjuvant therapy for patients with borderline resectable pancreatic cancer is undefined. Herein we report the outcomes of an extended neoadjuvant chemotherapy regimen in patients presenting with borderline resectable adenocarcinoma of the pancreatic head.

Methods. Patients identified as having borderline resectable pancreatic head cancer by American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology consensus criteria from 2008 to 2012 were tracked in a prospectively maintained registry. Included patients were initiated on a 24-week course of neoadjuvant chemotherapy. Medically fit patients who completed neoadjuvant treatment without radiographic progression were offered resection with curative intent. Clinicopathologic variables and surgical outcomes were collected retrospectively and analyzed.

Results. Sixty-four patients with borderline resectable pancreatic cancer started neoadjuvant therapy. Thirty-nine (61 %) met resection criteria and underwent operative exploration with curative intent, and 31 (48 %) were resected. Of the resected patients, 18 (58 %) had positive lymph nodes, 15 (48 %) required en-bloc venous resection, 27 (87 %) had a R0 resection, and 3 (10 %) had a complete pathologic response. There were no postoperative deaths at 90 days, 16 % of patients had a severe complication, and the 30-day readmission rate was 10 %. The median overall survival of all 64 patients was 23.6 months, whereas that of unresectable patients was 15.4 months. Twenty-five of the resected patients (81 %) are still alive at a median follow-up of 21.6 months.

Conclusions. Extended neoadjuvant chemotherapy is well tolerated by patients with borderline resectable pancreatic head adenocarcinoma, selects a subset of patients for curative surgery with low perioperative morbidity, and is associated with favorable survival.

Pancreatic ductal adenocarcinoma is the fourth leading cause of cancer-related death in the United States, with a 5-year survival of less than 6 %.[1] Half of patients present with metastatic disease with a median overall survival of 4–9 months.[2,3] Surgical resection followed by adjuvant therapy is associated with a more favorable median overall survival of 18–23 months and a 5-year survival rate of 18–20 %.[4–7] Unfortunately, only 10–20 % of patients present with resectable disease.[3] The remaining 25 % of patients have tumors that involve local vascular structures precluding resection and have been designated as locally advanced.[8]

Current consensus statements have recommended that resection be attempted in patients with locally advanced pancreatic cancer only if the celiac trunk is uninvolved and the superior mesenteric artery is not encased and as long as involved mesenteric veins can be resected and reconstructed safely.[9] This potentially operable subset of locally advanced disease has been recently referred to as "borderline resectable." Recent metaanalyses suggest that neoadjuvant therapy can help achieve a 25–33 % resection rate in borderline disease with an associated median overall survival of 18–21 months, but it was initially thought to negatively affect postoperative outcomes.[10–13] However,

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several groups have shown that patients completing neoadjuvant treatment before surgery seem to have a lower incidence of positive resection margins and local recurrence.[14–17] Neoadjuvant therapy also guarantees that all patients considered for surgery receive their course of chemotherapy, radiotherapy, or both. This is in contrast to the 24 % of resected patients who never receive their prescribed adjuvant therapy because of postoperative complications.[18] Additionally, neoadjuvant therapy may identify those patients with particularly aggressive disease who would likely not benefit from resection.[19,20]

Although there is increasing evidence supporting neoadjuvant therapy in borderline resectable disease, there is no accepted standard of care. Large randomized control trials suggested that gemcitabine has equivalent survival to fluoropyrimidines in the adjuvant setting, with gemcitabine having fewer toxicities.[4,21] However, combination therapies seem to elicit more tumor response rates by radiographic measurement and have higher resection rates in borderline resectable disease than monotherapy.[10] Most neoadjuvant protocols are administered over a 2- to 3-month period and often include radiotherapy.[22,23] Currently, there is no level 1 evidence that supports radiation as a necessary component of neoadjuvant therapy, nor is there a consensus on the optimal length of chemotherapy. This study was undertaken to examine an extended 24-week course of neoadjuvant gemcitabine and docetaxel in patients with borderline resectable pancreatic cancer where chemoradiation was flexibly used. This regimen was chosen on the basis of our previous success using gemcitabine-docetaxel combination therapy in advanced, unresectable pancreas cancer.[24] We hypothesized that this regimen may improve rates of margin-negative resection without negatively affecting perioperative outcomes in the neoadjuvant setting.

METHODS

Patient Selection Criteria

Patients evaluated from 2008 to 2012 with borderline resectable pancreatic head cancer by a multidisciplinary tumor board were offered extended neoadjuvant chemotherapy. Patients were tracked in a prospectively maintained database with institutional review board approval. Clinical variables were collected by retrospective review of the electronic medical record and/or billing data based on International Classification of Diseases 9th revision or Current Procedural Terminology codes. Baseline staging included a thin-slice pancreatic protocol computed tomography scan, chest X-ray or chest computed tomography, and a diagnostic laparoscopy with peritoneal washings. The diagnosis of cancer was confirmed by tissue biopsy before chemotherapy initiation. Patients were excluded from analysis if they were found to have metastatic disease at initial staging or they received any element of neoadjuvant therapy at an outside institution. Those with biliary obstruction were stented with a metal endoprosthesis before therapy.

Neoadjuvant Chemotherapy Regimen

Eligible patients were started on an eight-cycle course of 1,000 mg/m^2 of gemcitabine and 80 mg/m^2 of docetaxel given on days 1 and 8, every 21 days, with intermittent restaging by computed tomographic scan and cancer antigen (CA) 19–9 levels. Patients experiencing significant toxicity with gemcitabine and/or docetaxel were switched to second-line agents (5-fluorouracil, capecitabine, oxaliplatin, and/or irinotecan). After completing the neoadjuvant regimen, patients were restaged and considered for surgical resection if their disease had not progressed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and were medically fit for surgery.[25] Radiotherapy (50.4 Gy given over 28 fractions) was given preoperatively if the tumor was found to be progressing locally or if medical comorbidity temporarily precluded resection. Patients downstaged with chemoradiotherapy were also included for analysis on an intention-to-treat basis. Patients with metastatic disease at restaging were offered palliative chemotherapy.

Surgical Resection

Patients with borderline resectable pancreatic cancer by American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology consensus criteria at restaging were offered pancreaticoduodenectomy or total pancreatectomy.[9] Venous resection and reconstruction was performed whenever tumor or inflammation was believed to involve portomesenteric veins. The head and uncinate was separated from the superior mesenteric artery by using either a posterior or anterior "artery-first approach" so as to minimize cross-clamp time during portovenous reconstruction.[26,27] Complications were graded according to the Clavien–Dindo scoring system and dichotomized with a cutoff of grade III.[28] Postoperative pancreatic fistulas were graded according to the International Study Group on Pancreatic Fistulas consensus criteria.[29]

Pathology

Surgical specimens were inked along six margins by the pathologist in the presence of the surgeon according to a modified Leeds protocol.[30] The specimen was then sectioned in 3- to 4-mm slices with an average of 15 paraffin blocks created per specimen. Surgical resection margins

were considered positive if microscopic tumor was present within 1.0 mm of any inked margin. Tumor grading and staging were performed according to the 7th edition of the American Joint Committee on Cancer staging manual.[31]

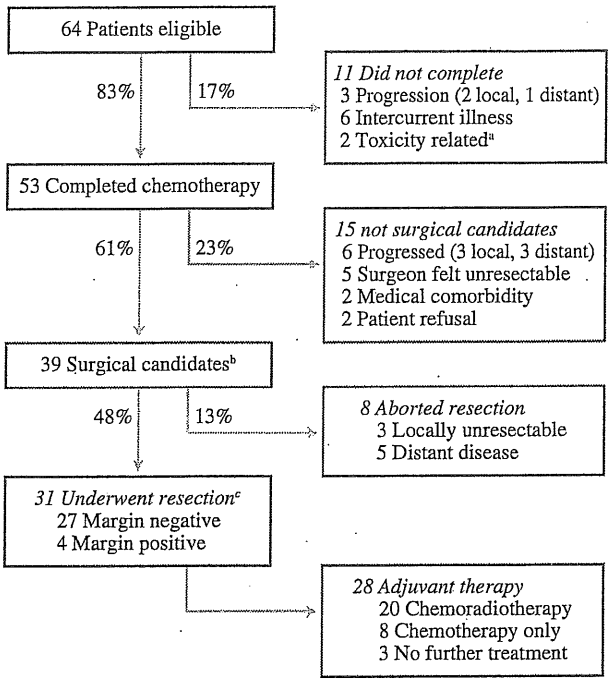
Statistical Analysis

Comparison of categorical variables was performed by a Fisher's exact test, and continuous variables were analyzed by Mann–Whitney rank-sum tests. Statistical significance was defined as having a P value of ≤ 0.05. Kaplan–Meier curves were used to determine survival, with the date of neoadjuvant initiation as time 0. Statistical analysis was performed with MedCalc 12.7 software (Mariakerke, Belgium).

RESULTS

Patient Selection

Sixty-four patients with borderline resectable pancreatic head cancer met the study criteria. Fifty-three (83 %) patients completed 24 weeks of neoadjuvant therapy, 15 (23 %) were determined to be unresectable at final re-staging, and thirty-nine (61 %) underwent abdominal exploration with an attempt at resection. This included a patient who was unable to continue chemotherapy to 24 weeks but had stable disease by RECIST. Eight patients were found to be unresectable intraoperatively, resulting in 31 (48 %) patients who were resected for cure. An expanded treatment schema is depicted in Fig. 1.



[a] Includes 1 patient with a death secondary to Stevens-Johnson Syndrome
[b] Includes 1 patient with a stable disease by RECIST who did not receive final cycle due to psychological inability to tolerate chemotherapy
[c] Includes 2 patients that received neoadjuvant chemoradiotherapy

FIG. 1 Treatment schema. Sixty-four patients with borderline resectable pancreatic head cancer met study inclusion criteria. Fifty-three patients (83 %) completed 24 weeks of neoadjuvant therapy, and 31 (48 %) had a resection with curative intent

Baseline Characteristics

Patient demographics, clinical stage of tumor, biliary stent use, and length of follow-up are shown in Table 1 for the entire cohort and subdivided according to resectability. The resected and unresectable groups showed no significant differences. The unresectable cohort tended to have more arterial involvement, but this was not statistically significant. Seventy-six percent of all patients had a pre-operative biliary stent placed.

Chemotherapy Response

Neoadjuvant treatment characteristics, chemotoxicity, serum CA19-9 level, and tumor response by RECIST are shown in Table 2. The median time from tissue diagnosis

TABLE 1 Baseline characteristics of all patients administered extended neoadjuvant chemotherapy

Characteristic	All patients ($n = 64$)	Resected ($n = 31$)	Unresectable ($n = 33$)	P value
Age at diagnosis, years	66 (61–73)	65 (60–70)	70 (62–75)	0.053
Male sex, n (%)	35 (55)	16 (52)	19 (58)	0.802
ECOG status > 1, n (%)	8 (13)	3 (10)	5 (15)	0.709
Arterial involvement, n (%)	23 (36)	8 (26)	15 (45)	0.123
Biliary stent, n (%)	48 (75)	23 (74)	25 (76)	1
Follow-up, months	15.8 (10.8–24.5)	21.6 (13.5–32.3)	13.4 (8.6–17.9)	0.004

Data are presented as the median (interquartile range) unless otherwise indicated. The Fisher's exact test was used for comparison of dichotomous variables and the Mann–Whitney test for continuous variables. Statistical significance of difference between resected and unresectable cohorts was defined as a P value of >0.05

ECOG Eastern Cooperative Oncology Group

TABLE 2 Tumor response to extended neoadjuvant chemotherapy

Characteristic	All patients ($n = 64$)	Resected ($n = 31$)	Unresectable ($n = 33$)	P value
Diagnosis to chemotherapy initiation, days	34 (22–58)	35 (25–55)	30 (20–68)	0.793
Length of chemotherapy, months	5.9 (5.5–6.2)	5.9 (5.7–6.2)	5.8 (4.3–6.1)	0.165
Completed chemotherapy, *n* (%)	53 (83)	30 (97)	23 (70)	0.006
Changed agents because of toxicity, *n* (%)	7 (11)	6 (19)	1 (3)	0.05
Initial CA19-9, U/mL	357 (100–999)	355 (107–1062)	445 (96–837)	0.856
Never had CA19-9 > 37 U/mL, *n* (%)	10 (16)	5 (16)	5 (15)	1
>50 % Drop in CA19-9, *n* (%)	41 (76)	25 (96)	16 (57)	0.001
Initial tumor size, cm	3.0 (2.4–3.5)	2.9 (2.4–3.5)	3.1 (2.7–3.6)	0.242
Change in tumor size by RECIST criteria				
Progressed, *n* (%)[a]	8 (12.5)	0 (0)	9 (27)	0.001
Stable, *n* (%)	29 (45)	14 (45)	15 (46)	1
Partial, *n* (%)	19 (30)	12 (39)	7 (21)	0.173
Complete, *n* (%)	8 (12.5)	5 (16)	2 (6)[b]	0.24

Data are presented as the median (interquartile range) unless otherwise indicated. The Fisher's exact test was used for comparison of dichotomous variables and the Mann–Whitney test for continuous variables. Statistical significance of difference between resected and unresectable cohorts was defined as a P value of >0.05

[a] Four patients progressed because of the development of metastatic lesion(s)

[b] One patient had metastatic disease found at attempted resection, and one had medical comorbidity precluding resection

to initiation of chemotherapy and length of neoadjuvant treatment were not statistically different between resected and unresected patients. However, a larger percentage (97 vs. 70 %; $P = 0.006$) of resected patients were able to complete all 24 weeks of neoadjuvant therapy, although 6 patients required alteration in one or more chemotherapeutic agents because of side effects. Whereas each group started with a similar median serum CA19-9, the resected cohort had a statistically larger percentage of patients with a greater than 50 % decrease of the biomarker at restaging compared with unresectable patients (96 vs. 57 %; $P = 0.001$). Tumor response by RECIST criteria was significantly more robust in the resected cohort compared with unresectable patients (55 vs. 27 %; $P = 0.042$).

Perioperative Outcomes

Preoperative, intraoperative, and postoperative patient and tumor characteristics are shown in Table 3. The median time from tissue diagnosis to resection was 8.2 months. Patients had a median American Society of Anesthesiologists (ASA) class of 3 and a median Charlson comorbidity index of 4. Two received neoadjuvant radiotherapy for local control. The median resection time was 8.5 h, with a median estimated blood loss of 300 mL, and 48 % of patients required a concomitant venous resection. There were no arterial resections. Resected patients had a median length of stay of 8.3 days, an overall complication rate of 58 %, a pancreatic fistula rate of 16 % (3 grade A, 1 grade B, and 1 grade C), a 30-day hospital readmission rate of 10 %, and no deaths within 90 days of surgery. The median resected specimen had a tumor size of 2.0 cm with 16 lymph nodes collected (58 % positive). Perineural or lymphovascular invasion was common, with 63 and 40 %, respectively. Twenty-seven (87 %) patients had a margin-free resection (R0), and 3 (10 %) of these had a complete pathologic response. Positive margins on 4 specimens included the portal vein groove ($n = 2$), the superior mesenteric vein groove ($n = 2$), the posterior surface ($n = 1$), and the anterior surface ($n = 1$). Adjuvant therapy was administered to 28 (90 %) resected patients (20 chemoradiotherapy and 8 chemotherapy only). Recurrence has been documented in 14 (45 %) of resected patients (4 local and 10 distant), and 17 (55 %) remain disease free at a median follow-up of 21.4 months.

Survival

Survival data for the entire cohort, attempted resections, and resected and unresectable patients are shown in Fig. 2. The median overall survival for the entire cohort was 23.6 months. Of those found to be unresectable, the median overall survival was 15.4 months. Median overall survival for both the attempted resection and resected cohorts were unable to be calculated because 75 and 81 % of patients within these groups were still alive at a median follow-up time of 20.4 and 21.6 months, respectively. The 1- and 2-year overall survival rates were 100 and 85 % in the resected cohort and 66 and 20 % in the unresectable cohort. Disease-free survival for the resected cohort was

TABLE 3 Perioperative characteristics of resected patients ($n = 31$)

Variable	Result
Preoperative	
Time from diagnosis to resection, months	8.2 (7.6–8.8)
Received preoperative radiotherapy, *n* (%)	2 (6)
ASA	3 (2–3)
Charlson comorbidity index[a]	4 (4–5)
Intraoperative	
Operative time, min[a]	510 (460–580)
Pylorus-preserving Whipple, *n* (%)	16 (52)
Standard Whipple, *n* (%)	14 (45)
Total pancreatectomy, *n* (%)	1 (3)
Vein resection, *n* (%)	15 (48)
Estimated blood loss, mL[a]	300 (250–520)
Transfused, *n* (%)	3 (10)
Pathologic	
Tumor size, cm	2.0 (1.1–2.9)
Number of lymph nodes resected	16 (13–21)
Positive lymph nodes, *n* (%)	18 (58)
Perineural invasion, *n* (%)[a]	19 (63)
Lymphovascular invasion, *n* (%)[a]	12 (40)
R0 resection (>1.0 mm clear margin), *n* (%)[b]	27 (87)
Pathologic complete response, *n* (%)	3 (10)
Postoperative	
Clavien–Dindo grade 1–2 complication, *n* (%)	13 (42)
Clavien–Dindo grade 3+ complication, *n* (%)	5 (16)
Postoperative pancreatic fistula, *n* (%)	5 (16)
Grade A, *n* (%)	3 (10)
Grade B, *n* (%)	1 (3)
Grade C, *n* (%)	1 (3)
90-day death, *n* (%)	0 (0)
Postoperative length of stay, days	8.3 (7.2–10.1)
Hospital-associated charges, dollars[a]	66,900 (62,100–79,300)
30-day readmission, *n* (%)	3 (10)
Disposition	
Home, *n* (%)	27 (87)
Home health, *n* (%)	2 (6.5)
Skilled nursing facility/rehab/hospice, *n* (%)	2 (6.5)
Recurrence	
Local, *n* (%)	4 (13)
Distant, *n* (%)[c]	10 (32)
Disease free, *n* (%)[c]	17 (55)

Data are presented as the median (interquartile range) unless otherwise indicated. The Fisher's exact test was used for comparison of dichotomous variables and the Mann–Whitney test for continuous variables.

[a] Thirty data points were available for analysis

[b] Includes two patients receiving neoadjuvant chemoradiotherapy

[c] Includes one patient receiving neoadjuvant chemoradiotherapy

23.2 months, with 9 (64 %) of patients with recurrent disease still living.

DISCUSSION

Neoadjuvant therapy for borderline resectable pancreatic cancer is being widely investigated as a potential strategy for downstaging initially unresectable patients and allowing for curative surgical treatment. Most regimens consist of 2–3 months of 5-fluorouracil-based or gemcitabine-based chemoradiotherapy and have converted approximately a third of patients to be resected with an associated median overall survival of 18–21 months.[10,11] The present data suggest that an extended 24-week chemotherapy regimen of gemcitabine and docetaxel is associated with a higher resection rate, favorable surgical outcomes, and potentially improved survival when compared with recent published reports in similar patients.

Despite a longer neoadjuvant chemotherapy course than is often used, only 3 % (2 of 67 patients) did not complete the regimen because of toxicity, thereby demonstrating the feasibility of this approach. Even though 11 patients (16 %) did not finish the 24-week protocol, this was an improvement over the published failure rate of 25 %.[10,23] Although the initial serum CA19-9 level was comparable between groups, the percentage of patients with a greater than 50 % decline in their biomarkers was significantly higher in the resected cohort (96 vs. 57 %; $P = 0.001$). This is in line with recent reports suggesting that CA19-9 is a positive predictor of chemotherapy response, resectability, and overall survival in pancreatic cancer.[32,33] The decrease in tumor size by RECIST criteria was significantly higher in the resected group (34 vs. 9 %; $P = 0.019$). When the entire cohort is considered, only 8 of 64 (13 %) patients progressed by RECIST, compared with 21–32 % progression rates reported in a recent meta-analyses.[10,11] Unfortunately, some patients may develop occult metastatic disease in the absence of local progression of the primary tumor; 4 (6 %) such patients had this finding in our study.

Thirty-nine of 64 (61 %) eligible patients were explored with curative intent, and 31 (48 %) had their tumors surgically extirpated. These results are more favorable than previously published rates of exploration (46–47 %) and resection (31–33 %) obtained with shorter regimens.[10,11] Therefore, we do not believe that we have missed any opportunities for resection. Instead, we have carefully selected those most likely to benefit from resection. Our 48 % rate of venous resection is well within the reported 12–65 % range for pancreatic cancer resections for locally advanced disease.[12] Neoadjuvant therapy did not affect the lymph node harvest, because resected specimens had a

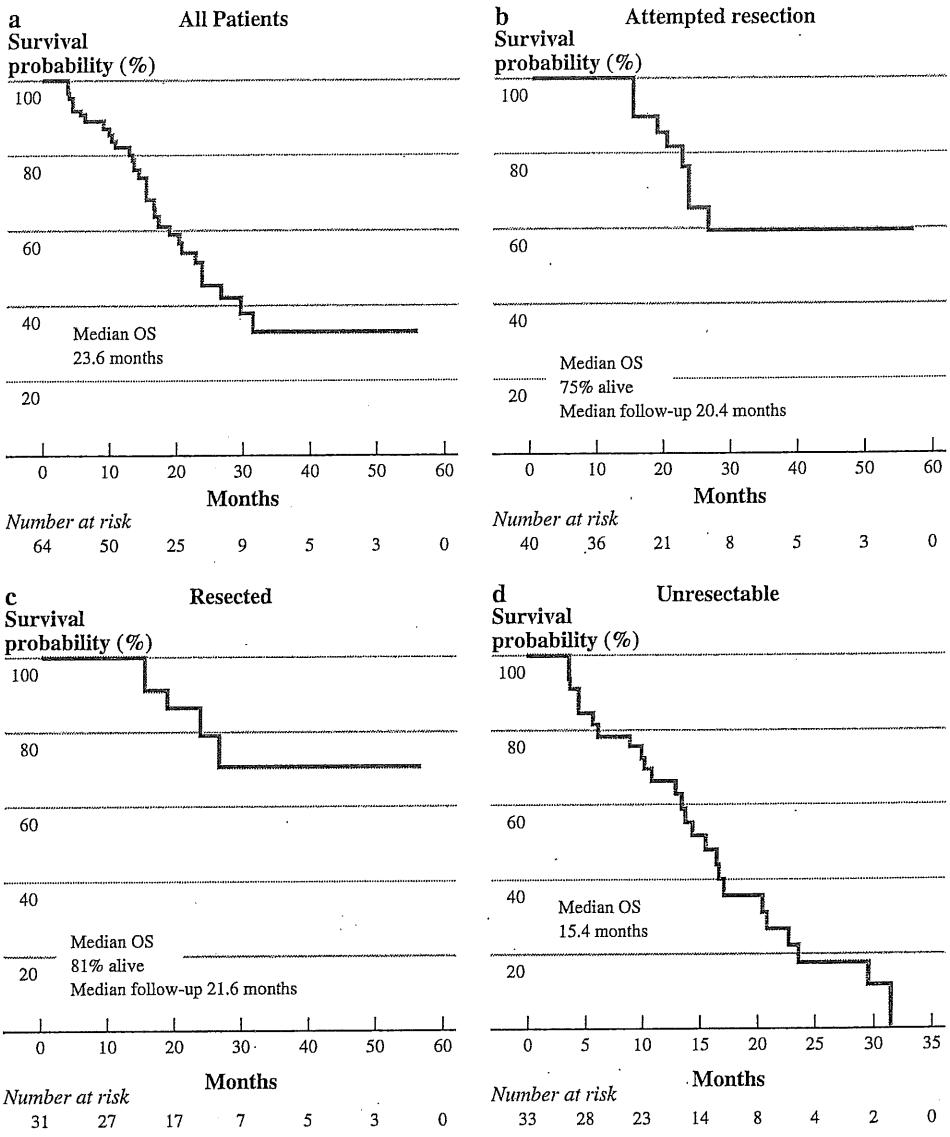


FIG. 2 Median overall survival. Kaplan–Meier curves showing survival data for **a** the entire cohort, **b** attempted resections, **c** patients with resections, and **d** patients with unresectable disease. The unresectable cohort includes patients with an attempted resection

median of 16 nodes, which is within current recommendations.[34,35] Many studies claim that the greatest predictor of overall survival after pancreatic head resection for adenocarcinoma is a negative margin.[36,37] Resection after extended neoadjuvant therapy resulted in 28 patients (87 %) having R0 resections, 3 of whom had a complete pathologic response. This result is consistent with the experience of M.D. Anderson and is a significant improvement over the R0 rates of 25–40 % reported by others.[30,38–40] This observation suggests that this regimen may have more activity or selects patients with more favorable biology than prior reports.

Although the operation often proved to be technically difficult, as reflected by the median operative time of 8.5 h, it was not associated with higher readmission, transfusion, or 90-day mortality rates than those reported in the literature.[41] The overall complication rate of 60 % is within the reported rate of 21–72 %; however, 16 % had Clavien–Dindo grade 3+ complications.[42] This low rate of serious surgical complications may reflect the selection bias created by the failure of patients with significant comorbidities to complete treatment. However, the pretreatment ASA class of 3 and Charlson comorbidity index of 4 suggest that this may not be as large a factor as previously thought. Our 16 % pancreatic fistula rate is within the reported ranges of 0–30 %, whereas the 0 % 90-day mortality rate is lower than the expected 2–6 %.[42–44] Patients were generally discharged home after 8 days, well below the reported average of 12–13 days after pancreatoduodenectomy.[41]

Whereas the perioperative outcomes in our study population were comparable to those reported by others, an important quality measure to judge any oncologic

operation is its effect on survival. The 1- and 2-year survival rates of 100 and 85 % in resected patients are improved compared with the published 1-year rate of 79–86 % and 2-year rate of 49–54 %.[10,11] Furthermore, the 15.4-month overall survival and associated 1- and 2-year survival rates of 66 and 20 % for unresectable patients are superior to the median overall survival of 8.4–10.2 months reported in large reviews.[10,11] The increased survival seen in the attempted resection cohort over all unresected patients likely represents an inherent selection bias created by the extended neoadjuvant therapy course for healthier patients and/or more biologically favorable disease.

The authors recognize limitations of this study, chief among them the retrospective nature of the data collection, the relatively small dataset, the absence of cost data and quality-of-life measures, its single-institution nature, and the limited follow-up time. Although a prospective list of eligible patients was maintained, an accounting of those who refused neoadjuvant treatment or were treated with alternative regimens at other institutions was not available. Additionally, because of the flexible use of preoperative or postoperative radiotherapy and nearly universal administration of adjuvant treatment, we cannot definitely attribute an improved median overall survival solely to our neoadjuvant strategy. However, because there are no current trials on the perioperative treatment of pancreas cancer, we felt compelled to administer additional adjuvant therapy in our cohort because there is level I evidence to support it.[4,6,21,45]

Conclusions

In summary, we have shown that extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer can be administered without significant perioperative complications and may be associated with an improved survival over published reports. The role for neoadjuvant treatment in this disease is evolving, and this study may offer some evidence that it should be pursued for those with borderline resectable disease. Although longer follow-up of the current cohort will better establish its efficacy, we believe the outcomes observed to date justify that the merits of this approach should be investigated further through a prospective randomized controlled clinical trial.

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