
Borderline Resectable Pancreatic Cancer: The Importance of This Emerging Stage of Disease

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- BACKGROUND:** Patients with borderline resectable pancreatic adenocarcinoma (PA) include those with localized disease who have tumor or patient characteristics that preclude immediate surgery. There is no optimal treatment schema for this distinct stage of disease, so the role of surgery is undefined.
- STUDY DESIGN:** We defined patients with borderline resectable PA as fitting into one of three distinct groups. Group A comprised patients with tumor abutment of the visceral arteries or short-segment occlusion of the Superior Mesenteric Vein. In group B, patients had findings suggestive but not diagnostic of metastasis. Group C patients were of marginal performance status. Patients were treated initially with chemotherapy, chemoradiation, or both; those of sufficient performance status who completed preoperative therapy without disease progression were considered for surgery.
- RESULTS:** Between October 1999 and August 2006, 160 (7%) of 2,454 patients with PA were classified as borderline resectable. Of these, 125 (78%) completed preoperative therapy and restaging, and 66 (41%) underwent pancreatectomy. Vascular resection was required in 18 (27%) of 66 patients, and 62 (94%) underwent a margin-negative pancreatectomy. A partial pathologic response to induction therapy (< 50% viable tumor) was seen in 37 (56%) of 66 patients. Median survival was 40 months for the 66 patients who completed all therapy and 13 months for the 94 patients who did not undergo pancreatectomy ($p < 0.001$).
- CONCLUSIONS:** This is the first large report of borderline resectable PA and includes objective definitions for this stage of disease. Our neoadjuvant approach allowed for identification of the marked subset of patients that was most likely to benefit from surgery, as evidenced by the favorable median survival in this group. (J Am Coll Surg 2008;206:833–848. © 2008 by the American College of Surgeons)
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Patients with American Joint Committee on Cancer (AJCC) stage I and II pancreatic adenocarcinoma who are treated with multimodality therapy including surgery have a median survival that may exceed 2 years and a potential

for cure.¹ But surgery is not an option for patients who initially present with locally advanced (AJCC stage III) disease. Indeed, for these patients, the median survival is usually less than 12 months despite the use of chemotherapy, chemoradiation, or both.² If the primary tumor cannot be surgically removed, longterm survival is uncommon, and it is generally believed that cure is not possible because currently available nonsurgical therapies rarely result in a complete histologic response.

Over the past several years, a distinct subset of patients with pancreatic cancer has been described: patients with “borderline resectable” tumors. Patients with borderline resectable disease comprise a subset that clarifies the imprecise continuum between radiologically and technically resectable and unresectable disease. The National Comprehensive Cancer Network (NCCN) previously acknowledged borderline resectable pancreatic adenocarci-

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Abbreviations and Acronyms

AJCC	= American Joint Committee on Cancer
CA 19-9	= cancer antigen 19-9
PA	= pancreatic adenocarcinoma
PV	= portal vein
SMA	= superior mesenteric artery
SMV	= superior mesenteric vein

noma as a unique substage of pancreatic cancer.³ But a thorough understanding of this group of patients has been elusive because of inconsistencies and imprecision in both the definitions and treatment philosophies that have been adopted in different centers. In an attempt to clarify these issues, we recently proposed an objectively defined, CT-based classification for tumors of the pancreatic head, neck, and proximal body, consistent with the current AJCC staging system, which clearly distinguishes borderline resectable from both resectable and locally advanced primary tumors.⁴ In this system, borderline tumors are defined as those that abut the superior mesenteric artery (SMA), abut or encase the common hepatic artery over a short segment, or occlude the superior mesenteric vein (SMV)-portal vein (PV) confluence, with suitable vein above and below such that venous reconstruction is possible. In addition to this established anatomic definition of borderline resectable, our evolving experience in the multidisciplinary management of localized pancreatic cancer has brought to light two additional subsets of patients who often escape accurate classification into a specific stage of disease: patients with indeterminate or questionable metastatic disease and patients with a suboptimal performance status or extensive medical comorbidities requiring prolonged evaluation that preclude immediate major abdominal surgery. Inclusion of these latter two groups into the borderline resectable category allows for accurate staging of all patients who present with newly diagnosed pancreatic cancer and specifically, the identification of a subset of patients who are marginally resectable or operable based on anatomic or clinical criteria. Such classification of patients by stage is necessary to allow for stage-specific therapy both on- or off-protocol.

From a therapeutic standpoint, no standardized treatment strategy exists for any of these three subsets of patients with borderline resectable disease because until now, they have not been defined as an identifiable group nor have they been considered as individual subgroups. Patients with borderline resectable disease based on anatomic criteria are at higher than usual risk for perioperative complications owing to the additional complexity of surgery, are at high risk for early systemic failure because of the advanced nature of the primary tumor, and are at high risk for a

margin-positive resection with surgery alone. So we have advocated use of a multidisciplinary approach to these patients and use neoadjuvant systemic chemotherapy, chemoradiation, or both rather than operation as the initial treatment modality. Placing surgery last in the treatment sequence is done in an attempt to separate this population of patients into two groups: those with more rapidly progressive disease in whom surgery directed at the primary tumor would provide no clinical benefit or would carry prohibitive risk, and those in whom systemic and local treatment response increases the potential for both complete resection of the primary tumor and a more favorable survival.⁴ Likewise, we have approached the other two groups of patients with borderline resectable disease with an initial program of nonoperative therapy to avoid surgery in those with extrapancreatic metastatic disease or nonrecoverable performance status. After chemotherapy and chemoradiation, patients with an improved performance status, fully evaluated comorbidities, and the absence of evolving metastatic disease on posttreatment (preoperative) restaging are considered for pancreatic resection.

The objectives of this report were to present our expanded classification system for patients with borderline resectable disease and to evaluate the management and outcomes of patients prospectively defined as falling into one or more of The University of Texas MD Anderson Cancer Center's borderline resectable categories.

METHODS

Clinical data on all patients evaluated for pancreatic adenocarcinoma (PA) between October 1999 and August 2006 were retrieved from an institutional pancreatic tumor database prospectively maintained in the Department of Surgical Oncology. All patients had a pretreatment cytologic or histologic diagnosis of adenocarcinoma of the pancreas that was obtained or confirmed at our institution. Patients with invasive intraductal papillary mucinous neoplasms, mucinous cystadenocarcinomas, and other nonpancreatic adenocarcinomas of the periampullary region were excluded.

Baseline evaluation of all patients consisted of a detailed medical history and physical examination, complete blood count and blood chemistries, chest radiography, and multidetector contrast-enhanced CT of the abdomen. Laparoscopy was rarely performed as a separate staging procedure, but was selectively performed in patients at the time of anesthesia induction for planned pancreatectomy. Performance status was recorded using the Zubrod/Eastern Cooperative Oncology Group (ECOG) scale.⁵ Serum CA 19-9 levels were recorded at the time of referral to our institution; they were not obtained in all patients, particu-

larly during the early years included in this study. Patient age was recorded at the date of the first evaluation.

After initial assessment, patients were reviewed by our multidisciplinary pancreatic tumor study group to determine their stage of disease. All patients who were prospectively characterized as being borderline resectable were included in this analysis. The MD Anderson borderline resectable categories included three patient subsets as defined by the following clinical and radiographic characteristics. Type A: patients with borderline resectable tumor anatomy as defined on CT images to include one or more of the following findings: tumor abutment ($\leq 180^\circ$ of the circumference of the vessel) of the SMA or celiac axis; tumor abutment or encasement ($> 180^\circ$ of the circumference of the vessel) of a short segment of the hepatic artery, typically at the origin of the gastroduodenal artery; or short-segment occlusion of the SMV, PV, or SMV-PV confluence that was amenable to vascular resection and reconstruction because of a patent SMV and PV below and above the area of tumor-related occlusion (Fig. 1).⁴ Type B: patients with borderline resectable disease owing to a concern for possible extrapancreatic metastatic disease. This subgroup of borderline resectable patients included those with CT findings suspicious for, but not diagnostic of, metastatic disease and those with known N1 disease from either prereferral laparotomy or endoscopic ultrasonography-guided fine-needle aspiration. Type B patients may have had a technically resectable⁶ or a borderline resectable primary tumor as defined on CT images. Type C: patients with borderline resectable disease owing to a marginal performance status (Zubrod 3), or those with a better performance status and severe preexisting medical comorbidity thought to require protracted evaluation that precluded immediate operation. By definition, type C patients with a marginal performance status were thought to have reversible causes of their current symptoms (such as hyperbilirubinemia-induced anorexia and fatigue); patients judged to have no potential for eventual operation were not included. Type C patients were managed by our multidisciplinary group of physicians including a dedicated pancreas program dietician, physical therapists, and members of our internal medicine faculty in a dedicated internal medicine preoperative assessment clinic. Type C patients may have had a radiologically resectable or a borderline resectable primary tumor. For purposes of this analysis, all patients were assigned just one MD Anderson type; if a patient's radiographic and clinical findings warranted inclusion in more than one borderline subgroup, he or she was classified in priority of $C > B > A$ (for example, a patient with both MD Anderson type B and type C features would be classified as type C).

Treatment schema

All patients received initial treatment with chemotherapy, chemoradiation, or both. Treatment was generally administered off-protocol, but some patients were treated on protocols designed for patients with locally advanced disease. Therapy was administered either at our institution or under the care of the patient's referring oncologist. External-beam radiation therapy consisted of 50.4 Gy in 28 fractions or 30 Gy in 10 fractions. Concomitant chemotherapy consisted of 5-fluorouracil, paclitaxel, gemcitabine, or capecitabine at radiosensitizing doses. When systemic therapy was administered, it consisted of gemcitabine alone or in combination; some patients, particularly those treated most recently, received targeted agents. The most common treatment sequence was 2 to 4 months of systemic therapy followed by chemoradiation, with restaging evaluations every 2 months. Approximately 4 to 6 weeks after completion of all neoadjuvant therapy, patients underwent a restaging evaluation that included CT and a complete physiologic assessment to determine suitability for operation. Patients found on restaging evaluation to have no evidence of progressive disease and who could, in the opinion of the operating surgeon and the multidisciplinary treatment group, safely undergo major abdominal surgery, were brought to the operating room for planned resection of the primary tumor. The complete treatment algorithm is illustrated in Figure 2.

Pancreaticoduodenectomy and distal pancreatectomy were performed in a standard fashion, as previously described.^{7,8} Tangential or segmental resection of the SMV, PV, or SMV-PV confluence was performed when the operating surgeon could not separate the pancreatic head or the uncinate process from these vessels without leaving gross tumor on the vessel or risking uncontrolled venotomy.⁹ When limited involvement of the common hepatic artery was identified, segmental resection of this vessel was performed with primary anastomosis or interposition grafting. Patients found to have unresectable disease at operation, usually because of the presence of radiographically occult extrapancreatic disease, underwent surgical bypass as clinically indicated.

Operative time (incision to application of all wound dressings) and blood loss (in mL) were recorded from the anesthesia record. Major postoperative complications were defined as previously described.¹⁰ Hospital stay was calculated by considering the day of operation as day 1; the day of discharge was not counted as a hospital day.

Histopathologic evaluation and assessment of treatment response

Standardized pathologic evaluation of the surgical specimen was performed as previously described.^{1,11} The SMA

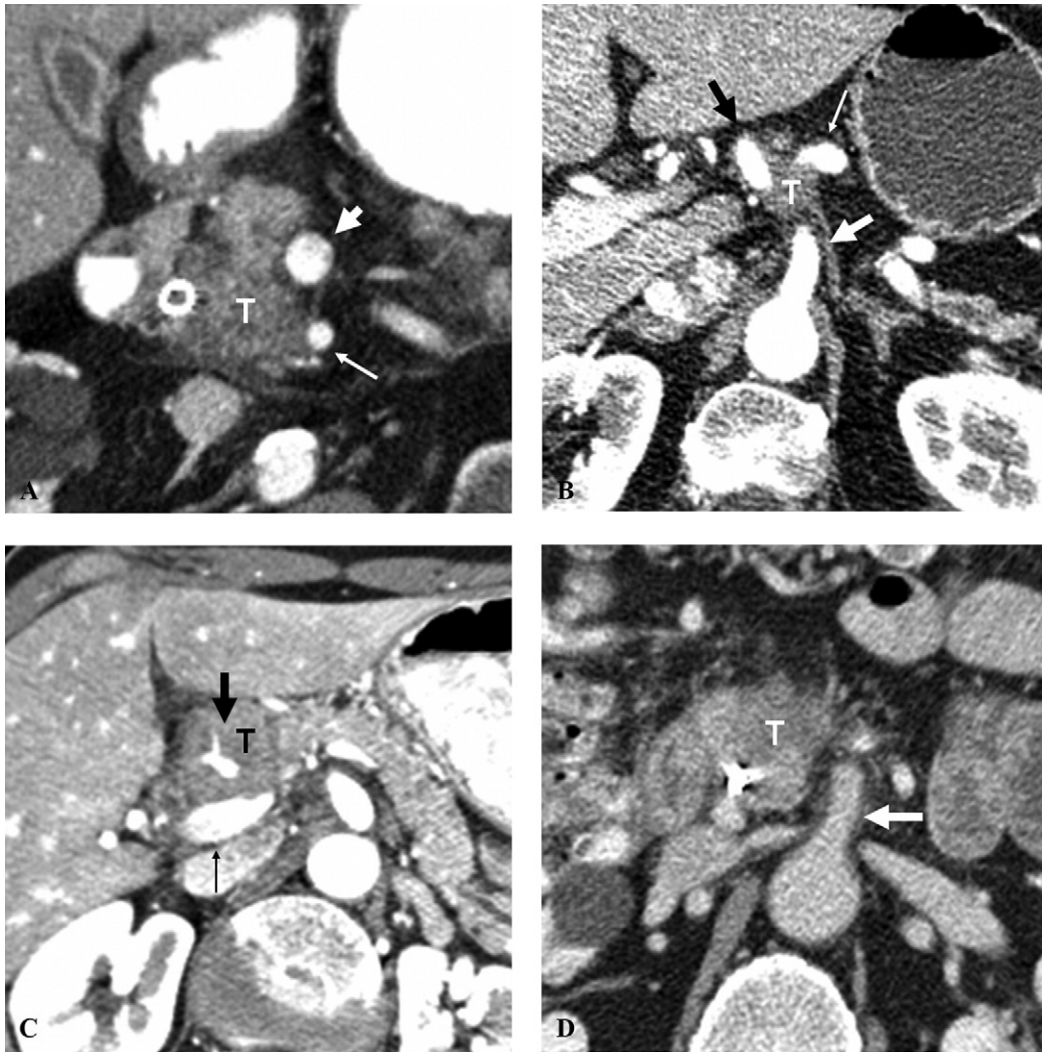
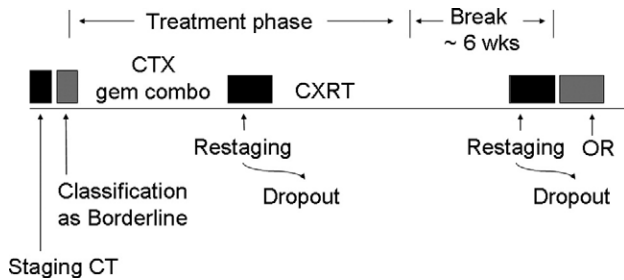


Figure 1. MD Anderson type A borderline resectable pancreatic adenocarcinoma (PA) as seen on multidetector CT imaging. (A) Initial CT scan obtained in a 78-year-old woman referred with unresectable PA that demonstrates abutment of the superior mesenteric vein (SMV) and superior mesenteric artery (SMA) by a mass in the uncinate process. After gemcitabine-based systemic therapy and external beam radiation, she underwent R0 pancreaticoduodenectomy. The specimen revealed a IIb treatment response¹³ and 17 lymph nodes negative for metastatic disease. She has no evidence of recurrence 26 months after initial diagnosis. T, tumor; thin arrow, SMA; thick arrow, SMV. (B) CT scan reveals a mass in the proximal body of the pancreas abutting the celiac axis in a 67-year old woman with biopsy-proven PA. After gemcitabine-based chemoradiation, she underwent R0 subtotal pancreatectomy. The specimen showed a IIb treatment response¹³ and five lymph nodes negative for metastatic disease. She is alive without disease 79 months after diagnosis. T, tumor; thick white arrow, celiac artery; thin white arrow, splenic artery; thick black arrow, common hepatic artery (CHA). (C) Staging CT scan from a 49-year old woman referred with unresectable pancreatic adenocarcinoma demonstrates encasement of the CHA at the origin of the gastroduodenal artery. After gemcitabine-based systemic chemotherapy and radiation, she underwent R0 pancreatectomy requiring tangential resection of the portal vein (PV) and segmental resection and reconstruction of the CHA. Twenty-three lymph nodes, all negative for tumor, were recovered. She is currently alive without disease 69 months after diagnosis. T, tumor; thick arrow, CHA and origin of gastroduodenal artery; thin arrow, PV. (D) CT image in the venous phase of contrast enhancement reveals short-segment occlusion of the SMV/PV in a 59-year-old man with biopsy-proven PA. The vein proximal and distal to the obstructed segment was patent. He received gemcitabine-based systemic chemotherapy followed by chemoradiation and then underwent R0 pancreaticoduodenectomy, with segmental resection and reconstruction of the SMV-PV confluence with an internal jugular vein interposition graft. The specimen revealed a IIb response¹³ to therapy and 15 lymph nodes negative for tumor. He suffered recurrence in the lung and bones 23 months after operation and died shortly thereafter. T, tumor; arrow, SMA; SMV not visualized because of occlusion at this level.



Staging CT

Figure 2. Treatment approach for patients with borderline resectable pancreatic adenocarcinoma. All patients undergo a comprehensive staging evaluation and an assessment of performance status (see text). Patients staged as borderline resectable are treated with induction chemotherapy, chemoradiation, or both. After preoperative therapy is complete, restaging is performed to select those patients most likely to benefit from operation. CTX, chemotherapy; CXRT, chemoradiation; gem combo, gemcitabine-based systemic agents; OR, taken to operating room for planned pancreatotomy.

margin was defined as the soft tissue margin directly adjacent to the proximal 3 to 4 cm of the SMA. In all patients, the SMA margin was evaluated according to the *AJCC Cancer Staging Manual* (6th edition) guidelines.¹² This margin was identified and inked by the surgeon and pathologist immediately on specimen removal and was evaluated by permanent-section microscopic examination; when tumor extended to the inked margin, the margin was considered positive. The technique for assessment of the SMA margin was the same regardless of whether vascular resection was performed. The pancreatic transection margin and the common bile/hepatic duct transection margins were evaluated by examining a complete en face section of each margin. At the discretion of the surgeon, these two margins were usually evaluated intraoperatively using frozen-section analysis, and if positive, additional bile duct or pancreatic parenchyma was usually resected. An operation was designated R0 if all final margins were negative (no tumor cells were identified at any of the three resection margins) and R1 if any of the final margins were microscopically positive (tumor cells were present at one or more of the margins).

Tumor size was calculated by the pathologist by measuring the maximum gross transverse diameter of the tumor after resection. This measurement was difficult to determine in some patients after preoperative therapy because the tumor was often hard to distinguish from uninvolved adjacent pancreatic parenchyma by gross examination.

The grade of neoadjuvant treatment effect was assessed on permanent sections by a faculty gastrointestinal pathologist and scored using a previously published grading system.¹³ A minimal pathologic response was defined as a treatment effect score of either grade I (90% or more viable tumor cells remaining after induction therapy) or IIa (50% to

89% remaining viable tumor cells). A partial pathologic response was defined as a treatment effect score of IIb (10% to 49% remaining viable tumor cells) or III (less than 10% remaining viable tumor cells). A treatment effect score of IV, indicating no remaining viable tumor cells, was used to designate a complete pathologic response.

Followup and statistical analysis

After completion of all treatment, patients were evaluated every 3 to 4 months by physical examination, chest radiography, and abdominal CT. In patients without evidence of disease after 2 years of followup, evaluations were reduced to 6-month intervals. The development of a new low-density mass in the region of the resected pancreas or root of mesentery was considered evidence of local recurrence, even in the absence of symptoms. Similarly, radiographic evidence of a new low-density mass in the liver or lungs was considered evidence of distant recurrence; biopsy was rarely performed for radiographic findings consistent with recurrent cancer. Peritoneal recurrence was defined as the finding of new ascites on physical examination or CT. Only the first site(s) of recurrent disease were documented for this study.

For all analyses involving CA 19-9, patients with serum levels of CA19-9 that were not measurable (patients with the Lewis a-b- blood group antigen who do not synthesize CA 19-9), patients with an elevated serum bilirubin (> 1.5 mg/dL), and patients who received prereferral chemotherapy or radiation were excluded. In an attempt to eliminate lead time bias, we also performed all analyses including and excluding those patients who underwent initial evaluation at MD Anderson more than 6 weeks after initial diagnosis. No marked difference in the results was obtained. So the results reported here reflect only the first three objective exclusionary criteria listed previously.

Overall survival was calculated from the date of cytologic or histologic diagnosis until the date of death or last contact; time to progression was calculated, only in patients who underwent resection, from the date of cytologic or histologic diagnosis until the date of recurrence or the last date at which the patient was known to be free of disease. The Kaplan-Meier method was used to generate survival curves by clinical characteristics. The log-rank test was used to assess differences between survival curves. Followup time was measured from time of diagnosis; the median was calculated for all patients who had not died by the time of last followup. All statistical tests were two-tailed, with a significance level of $p < 0.05$. SPSS software version 15.0 was used for all statistical analyses.

Table 1. Clinical and Demographic Characteristics of 160 Patients with Borderline Resectable Pancreatic Cancer

Characteristic	All patients	Borderline resectable type			p Value*
		A	B	C	
Total patients, n	160	84	44	32	
Age, y					
Median (mean)	63 (63)	60 (61)	61 (61)	73 (71)	0.001
Range	36–90	37–81	36–77	50–90	
Gender, n (%)					NS
Male	84 (52)	37 (44)	26 (59)	21 (66)	
Female	76 (48)	47 (56)	18 (41)	11 (34)	
Tumor location in pancreas, n (%)					NS
Head/uncinate	142 (89)	73 (87)	40 (91)	29 (91)	
Body/tail	18 (11)	11 (13)	4 (9)	3 (9)	
Prereferral laparotomy, n (%)	38 (24)	16 (19)	19 (43)	3 (9)	0.001
Bypass	31 (19)	12 (14)	16 (36)	3 (9)	0.003
Exploration only	7 (4)	4 (5)	3 (7)	0 (0)	NS
Prereferral therapy	12 (8)	7 (8)	5 (11)	0 (0)	NS
Systemic chemotherapy	6 (4)	3 (4)	3 (7)	0 (0)	NS
External-beam radiation	7 (4)	5 (6)	2 (5)	0 (0)	NS
Pretreatment CA19-9, U/mL					
All patients					
Median (mean)	212 (838)	190 (803)	269 (954)	324 (767)	NS
Range	2.3–11,482	2.3–11,482	9.1–7,194	13–3,787	
Patients who underwent pancreatectomy, n (%)					
Median (mean)	218 (961)	154 (1,138)	211 (773)	324 (831)	NS
Range	9–11,482	19–11,482	9–7,194	32–2,797	
Patients who did not undergo pancreatectomy					
Median (mean)	203 (746)	190 (582)	578 (1,159)	268 (730)	NS
Range	2–6,725	2–6,725	23–3,996	13–3,787	
Pancreatectomy performed, n (%)					
Yes	66 (41)	32 (38)	22 (50)	12 (38)	NS
No	94 (59)	52 (62)	22 (50)	20 (62)	

*p value for comparison between borderline resectable types.

RESULTS

Patient demographics and clinical variables

Between October 1999 and August 2006, 2,454 patients were evaluated at our institution for PA. Of these, 160 patients (7%) were prospectively characterized as having borderline resectable disease: 84 (52%) type A, 44 (28%) type B, and 32 (20%) type C (Table 1). The median age of these patients was 63 years (range 36 to 90 years). Patients classified as type C were substantially older (median 73 years) than type A or B patients (median 60 and 61 years; $p < 0.001$). Tumors were located in the pancreatic head or uncinate process in 142 (89%), and the body or tail in 18 (11%) of the 160 patients. Prereferral laparotomy with an unsuccessful attempt at tumor resection had been performed in 38 (24%) of the 160 patients, with half of these patients classified as type B ($p < 0.001$ when comparing the frequency of prereferral laparotomy between groups).

Chemotherapy or chemoradiation had been used before referral in 12 (8%) of 160 patients. Pretreatment serum levels of CA19-9 were evaluable in 105 (66%) of 160 patients; these patients had a median CA 19-9 level of 212 U/mL (range 2.3 to 11,482 U/mL). There was no difference in the initial pretreatment serum level of CA 19-9 between type A, B, and C patients.

Treatment

The treatment of all patients is summarized in Figure 3. Posttreatment preoperative restaging evaluation was not completed in 35 (22%) of the 160 patients. After initial evaluation, 9 (26%) of these 35 patients were lost to followup. These were patients who were sent back to their local oncologists after initial staging, multidisciplinary assessment with therapeutic recommendations, and a plan to return to MD Anderson for restaging. We believe that these

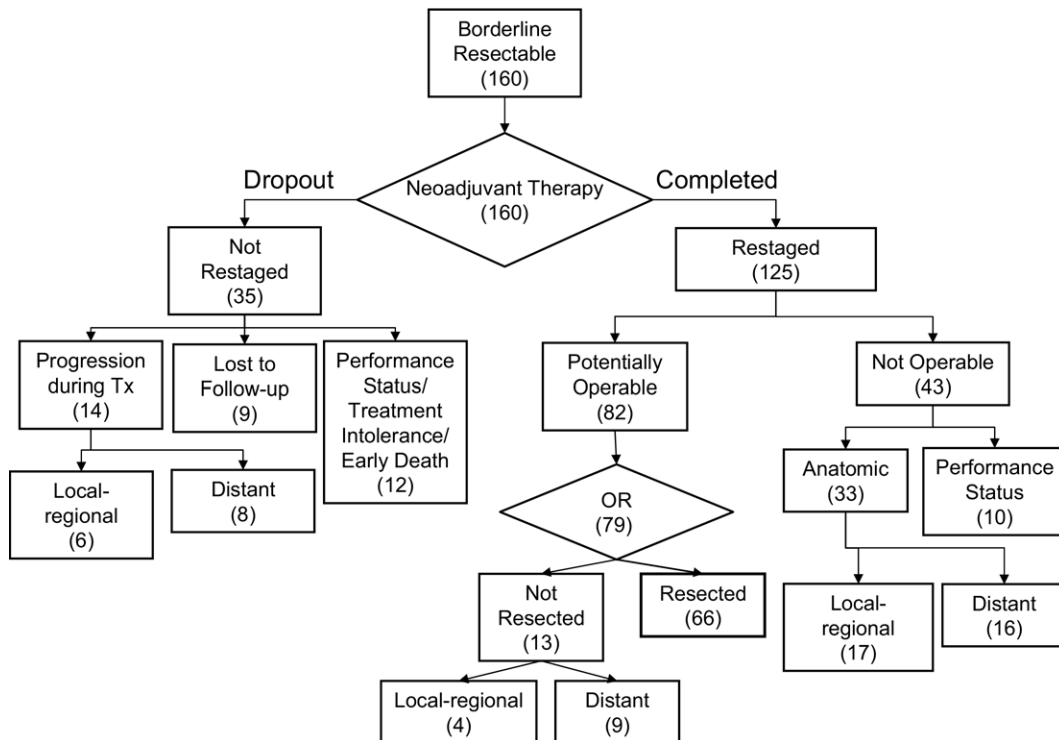


Figure 3. Treatment of 160 patients with borderline resectable pancreatic cancer. OR, operation; Tx, therapy.

patients did not return as a result of disease progression or a decline in performance status. Before completion of all planned neoadjuvant therapy or scheduled preoperative restaging, 14 (40%) of 35 patients had distant ($n = 8$) or local-regional ($n = 6$) disease progression. The remaining 12 patients (34%) tolerated the therapy poorly or suffered what was believed to be an irreversible decline in performance status; 6 of them died before restaging. Of these six deaths, four occurred after completion of all neoadjuvant therapy and were from disease progression ($n = 1$), complications associated with profound dehydration and acute renal failure ($n = 1$), cholangitis secondary to an occluded endobiliary stent ($n = 1$), and complications of small bowel obstruction ($n = 1$). The cause of death of two patients who died during initial treatment is unknown.

In total, 125 (78%) of the 160 patients underwent a complete restaging evaluation after a median of 15 weeks (range 10 days to 40 weeks) of induction therapy. The duration of neoadjuvant therapy was considerably shorter in type C patients (median 4 weeks, range 10 days to 34 weeks) than in either type A (median 16 weeks, range 2 to 40 weeks) or B patients (median 15 weeks, range 2 to 37 weeks, $p = 0.002$). During preoperative therapy, 82 (66%) of the 125 patients received systemic chemotherapy and 117 (94%) received chemoradiation. When prereferral therapy was included, 83 (66%) of 125 patients had re-

ceived systemic chemotherapy and 122 (98%) had received chemoradiation before preoperative restaging.

At the time of restaging evaluation, 43 (34%) of the 125 patients were determined to be ineligible for operation: 10 (23%) were believed to have a performance status insufficient for major abdominal surgery and 33 (77%) had CT evidence of distant disease progression ($n = 16$) or unresectable local-regional disease ($n = 17$). The remaining 82 patients (66%) had no evidence of metastatic disease and were determined to have tumor anatomy and a performance status suitable for operation. Of these 82 patients, 3 refused an operation; the remaining 79 patients (63% of the 125 who were restaged) were brought to the operating room for planned pancreatotomy. The median time from completion of neoadjuvant therapy to surgery in these 79 patients was 7 weeks (range 2 to 51 weeks). Of the 79 patients brought to surgery, 13 (16%) were found to have unresectable disease owing to the presence of radiographically occult distant metastases ($n = 9$) or locally advanced disease ($n = 4$), and 66 (53% of patients who underwent restaging) underwent a grossly complete resection of the primary tumor.

In total, 66 (41%) of 160 borderline resectable patients underwent pancreaticoduodenectomy ($n = 57$) or distal subtotal pancreatectomy ($n = 9$; Table 2). There was no statistically significant difference in the resectability rates

Table 2. Preoperative, Operative, and Histopathologic Data for 66 Patients Who Received All Therapy (Including Pancreatectomy)

Characteristic	All patients	Borderline resectable type			p Value*
		A	B	C	
Total patients, n	66	32	22	12	
Preoperative factors, n (%)					
Laparotomy before referral					
Bypass	14 (21)	4 (13)	7 (32)	3 (25)	NS
Exploration only	4 (6)	2 (6)	2 (9)	0 (0)	
Any neoadjuvant therapy [†]	66 (100)	32 (100)	22 (100)	12 (100)	
Systemic chemotherapy	49 (74)	24 (75)	19 (86)	6 (50)	NS
Chemoradiation	63 (95)	32 (100)	19 (86)	12 (100)	
Duration of neoadjuvant therapy, wk					
Beginning to end of therapy					
Median (mean)	15 (15)	16 (16)	17 (16)	11 (11)	NS
Range	1.1–40	2.4–40	2.3–37	1.1–34	
End of therapy to surgery					
Median (Mean)	6 (8)	6 (7)	7 (7)	8 (12)	NS
Range	2–51	2–18	3–15	5–51	
Restaging (preoperative) CA19-9, U/mL					
Median (mean)	40 (154)	31 (82)	42 (238)	46 (192)	NS
Range	7–2,908	7–566	8–2,908	27–960	
Operative factors					
Surgical procedure, n (%)					
Pancreaticoduodenectomy	57 (86)	28 (88)	19 (86)	10 (83)	NS
Distal subtotal pancreatectomy	9 (14)	4 (12)	3 (14)	2 (17)	
Operative time, h					
Median (mean)	6.8 (7.1)	7.5 (7.4)	6.2 (6.7)	6.2 (7.0)	NS
Range	2.9–12.9	3.8–12.9	3.1–10.4	2.9–12.9	
Estimated blood loss, mL					
Median (mean)	700 (850)	738 (977)	650 (785)	600 (633)	NS
Range	75–3,300	90–3,300	125–2,500	75–1,500	
Hospital stay, d					
Median (mean)	10 (11)	9 (11)	9 (12)	13 (12)	.03
Range	6–42	6–21	6–42	7–20	
Vascular resection, n (%)					
Hepatic artery	2 (3)	2 (3)	0	0	NS
SMV/PV	18 (27)	12 (38)	3 (14)	3 (25)	NS
Histopathologic factors, n (%)					
Treatment effect score [‡]					
I	0	0	0	0	
IIa	26 (40)	11 (34)	8 (36)	7 (58)	
IIb	25 (38)	12 (38)	9 (41)	4 (33)	NS
III	8 (12)	4 (13)	4 (18)	0	
IV	4 (6)	3 (9)	0	1 (8)	
Tumor size, cm					
Median (mean)	2.5 (2.6)	2.5 (2.5)	2.9 (2.7)	2.5 (2.5)	NS
Range	0.2–6	0.2–6	0.6–4.3	0.8–3.5	
Margin status					
R0	62 (94)	31 (97)	21 (95)	10 (83)	NS
R1	4 (6)	1 (3)	1 (5)	2 (17)	

(table continued)

Table 2. Continued

Characteristic	All patients	Borderline resectable type			p Value*
		A	B	C	
Lymph node status					
Patients with positive nodes, n (%)	26 (39)	12 (38)	8 (40)	6 (50)	NS
Lymph nodes reported, n [‡]					
Median (mean)	20 (21)	21 (21)	20 (20)	17 (19)	NS
Range	2–50	5–50	2–43	10–40	
Positive lymph nodes, n [†]					
Median (mean)	3 (3)	2 (3)	4 (6)	2 (2)	NS
Range	1–21	1–7	1–21	1–4	

Data are number of patients (%) unless otherwise specified.

*p value for comparison between borderline resectable types.

[†]Includes prereferral and postreferral treatment.

[‡]Treatment effect score was not available for three patients.

[§]Pancreaticoduodenectomy was associated with a higher number of lymph nodes retrieved (median 21, range 10–50) than was distal subtotal pancreatectomy (median 10, range 2–21, $p = 0.001$).

[¶]In patients with at least one positive lymph node.

NS, not significant; PV, portal vein; SMV, superior mesenteric vein.

between borderline resectable types. The 66 patients underwent operation a median of 22 weeks (range 7 to 65 weeks) after initiation of therapy, with no marked difference in the lengths of time from start of therapy to surgery between borderline resectable types. Venous resection was performed in 18 (27%) of 66 patients; 2 of these patients also required short-segment resection of the common hepatic artery. There was no difference in the percentage of patients who required vascular resection and reconstruction among the three borderline resectable types.

Among the 66 patients who underwent pancreatectomy, the median operative blood loss was 700 mL (range 75 to 3,300 mL), median operative time was 6.8 hours (range 2.9 to 12.9 hours), and median length of hospital stay was 10 days (range 6 to 42 days). There was no difference in median blood loss or median operative time between the three borderline resectable types, but type C patients had a longer median hospital stay than either type A or B patients ($p = 0.03$).

Additional postoperative adjuvant therapy was delivered to 13 (20%) of the 66 patients; chemoradiation was administered to the 2 patients who had not received it preoperatively, and the other 11 patients received systemic chemotherapy.

Toxicity and complications

Of 125 patients who underwent a complete restaging evaluation, endobiliary stent exchange was necessary during induction treatment or in the interval between induction treatment and restaging in 19 patients (15%), owing to stent occlusion or cholangitis. In total, 25 (20%) of the 125 patients required hospitalization before restaging. The primary indications for the 27 hospitalizations in these 25 patients were dehydration ($n = 8$), hematologic toxicity ($n = 2$), gastrointestinal tox-

icity ($n = 3$), low-grade sepsis ($n = 3$), and endobiliary stent occlusion ($n = 11$). It should be noted that toxicities recorded before restaging may have been incompletely reported, because not all patients received all therapy at our institution.

Major postoperative complications occurred in 13 (20%) of 66 patients who underwent pancreatectomy. Perioperative death occurred in two patients. The first of these was a 77-year-old, type C patient who underwent an uncomplicated pancreaticoduodenectomy but required an emergent return to the operating room on postoperative day 4 for intraabdominal hemorrhage; no discrete source of surgical bleeding was identified. Two days later, she suffered bilateral cerebral cortical infarcts, leading to a progressive neurologic decline and death on postoperative day 13. The other death occurred in a 54-year-old, type C patient who underwent pancreaticoduodenectomy with PV resection and reconstruction. After an uncomplicated postoperative course, she required readmission to the hospital 30 days after initial discharge for upper gastrointestinal hemorrhage secondary to an inferior pancreaticoduodenal artery pseudoaneurysm; this was successfully treated by exclusion with an SMA stent. Recurrent upper gastrointestinal hemorrhage localized to a pseudoaneurysm of the right hepatic artery subsequently developed. Despite successful embolization, she never recovered satisfactory end-organ function and died 5 months after pancreatectomy.

Other major complications of pancreatectomy included pulmonary embolus treated by anticoagulation ($n = 1$), abdominal wall dehiscence requiring reoperation ($n = 1$), upper gastrointestinal hemorrhage managed conservatively ($n = 1$), chylous drainage from an abdominal drain site that resolved spontaneously

Table 3. Rates of Resection, Pathologic Response, and Survival for 160 Patients with Borderline Resectable Pancreatic Cancer

MD Anderson borderline type	Patients						Median survival, mo			p Value [†]
	Total		Resected		Treatment effect IIb, III or IV*		All patients	Resected patients	Patients who did not undergo resection	
	n	%	n	%	n	%				
A	84	52	32	38	19	59	21	40	15	0.001
B	44	28	22	50	13	59	16	29	12	0.001
C	32	20	12	38	5	42	15	39	13	0.009
Total	160		66	41	37	56	18	40	13	0.001

*Percent of patients with that type of disease who underwent resection; treatment effect not reported in 3 of 66 patients who underwent pancreatectomy.

[†]p value for comparison of median survival times of resected and nonresected patients.

(n = 1), *Clostridium difficile* colitis (n = 2), intraabdominal fluid collection requiring percutaneous drainage (n = 1), transient acute pulmonary failure (n = 2), and cardiac tachyarrhythmia (n = 2).

Histopathology and treatment effect

All 66 patients who underwent surgical resection were confirmed to have PA on final pathologic analysis (Table 2). The median tumor size (measured at the time of pathologic assessment of the surgical specimen) was 2.5 cm (range 0.2 to 6 cm), with no difference between borderline resectable types. Surgical margins were grossly negative in all patients; 4 (6%) of 66 patients, all of whom underwent pancreaticoduodenectomy, were found to have microscopically positive SMA (n = 2), pancreatic (n = 1), or bile/hepatic duct (n = 1) margins on permanent histologic sections. The patient with a positive pancreatic margin had atypia on intraoperative frozen-section examination and underwent re-resection of the margin twice, but the permanent section margin was positive for invasive adenocarcinoma.

A median of 20 lymph nodes per specimen were examined (range 2 to 50 nodes), with a higher number of nodes retrieved and examined in patients who underwent pancreaticoduodenectomy (median 21; range 10 to 50) compared with patients who underwent distal subtotal pancreatectomy (median 10; range 2 to 21; p = 0.001). Lymph node metastases were identified in 26 (39%) of the 66 patients who underwent pancreatectomy, including 12 (38%) type A patients, 8 (40%) type B, and 6 (50%) type C. The percentage of patients with node-positive disease did not differ between borderline resectable types. Among patients with positive nodes, the median number of positive nodes was 3 (range 1 to 21).

The neoadjuvant treatment effect score was determined in 63 of the 66 resected patients; the score was not recorded in the final pathology report for the other 3 patients and the slides were not available for re-review. A partial or complete pathologic response to treatment (< 50% remaining viable

tumor cells; scores IIb, III, or IV) was found in 37 (56%) of the 66 patients who underwent resection (Table 3). The percentage of patients with a partial or complete pathologic response was similar across borderline resectable types. Four (6%) of the 66 patients had a complete pathologic response (grade IV); Recurrent metastatic pancreatic cancer later developed in 1 of them, 1 died of metastatic non-small cell carcinoma of the lung, and the other 2 remain without evidence of disease. The patient who died of metastatic lung cancer was thought to have a separate primary ductal adenocarcinoma of the pancreas based on the morphology and immunohistochemistry profile of the pancreatic tumor biopsy. The pretreatment biopsy material of the two patients currently without evidence of disease has been re-reviewed by the senior cytopathologists at MD Anderson. In one patient, the diagnosis was confirmed; in the other patient, there was no consensus about the presence or absence of adenocarcinoma on the pretreatment biopsy. But this patient had a serum level of CA19-9 > 600 U/mL at the start of systemic therapy (with a normal level of serum bilirubin), and it declined to 112.7 U/mL after systemic therapy and to 22.2 U/mL at the time of preoperative restaging after chemoradiation. This patient's CA19-9 remains within the normal range (21 U/mL) 2 years after pancreaticoduodenectomy.

Followup, survival, and recurrence

The median followup for patients who were alive at last followup was 25 months (range 2 to 88 months). For patients who completed all therapy including operation, the median followup of patients alive at last followup was 27 months (range 9 to 88 months). At the time of last followup, 110 (69%) of the 160 patients had died: 29 (44%) of 66 patients who completed all therapy including operation, and 81 (86%) of 94 patients who did not undergo surgical resection.

The median overall survival of all 160 patients with borderline resectable disease was 18 months, with a corre-

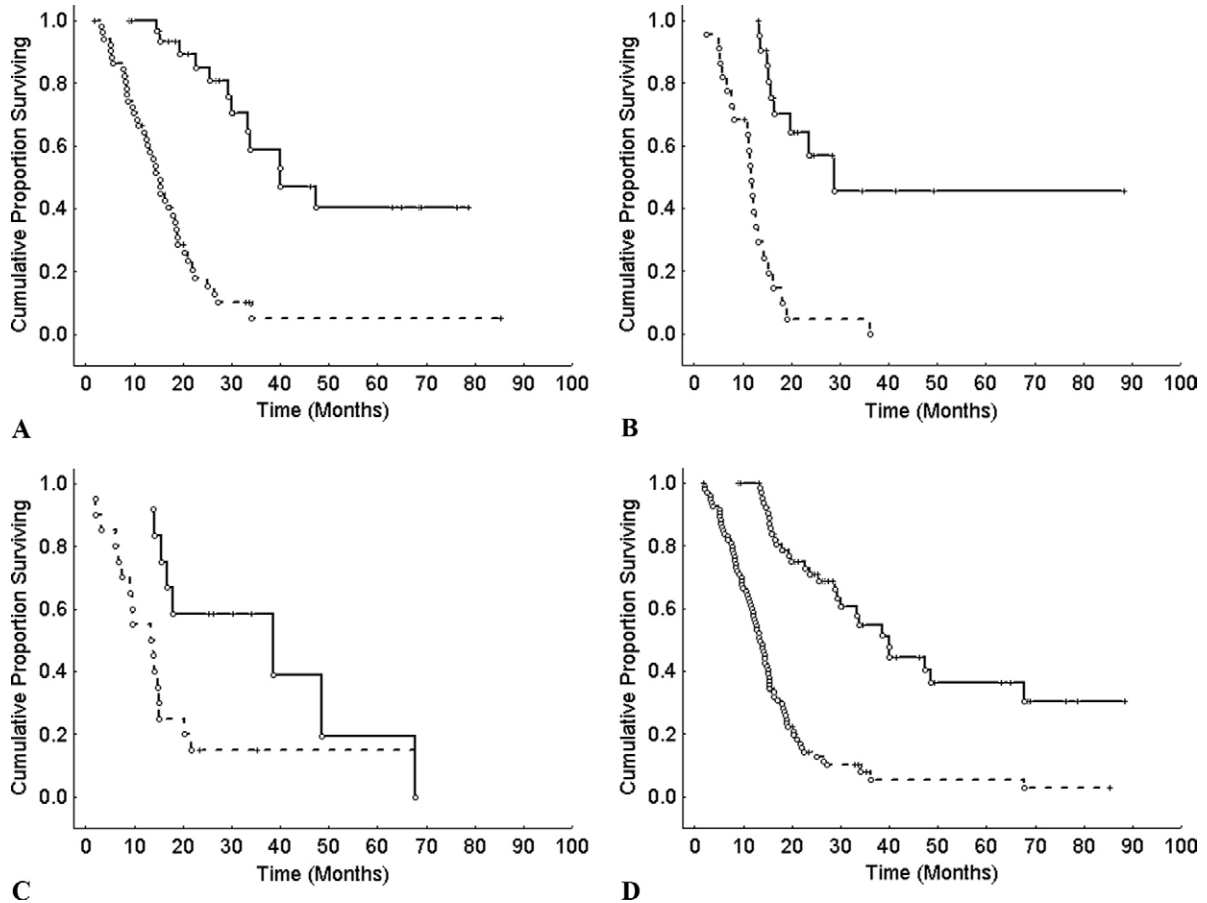


Figure 4. Kaplan-Meier actuarial overall survival curves for patients with resected and unresected pancreatic cancer for each borderline resectable subtype (A, type A; B, type B; C, type C), and for all 160 patients (D). In each group, patients who completed all therapy, including operation, had a substantial survival advantage compared with patients who did not undergo surgical resection. Solid line, patients who underwent resection; dotted line, patients who did not undergo resection; open circle, death; crosshatch, patient censored.

sponding 5-year overall survival rate of 18% (Table 3, Fig. 4). Patients of borderline resectable types A, B, and C had median overall survivals of 21, 16, and 15 months, respectively, with corresponding 5-year overall survival rates of 19%, 19%, and 16%, respectively.

The 66 patients who completed all therapy including resection had a median survival of 40 months and a 5-year overall survival rate of 36% (type A, 40 months/40%; type B, 29 months/46%; type C, 39 months/19%). In contrast, the 94 patients who did not undergo resection of the primary tumor had a median survival of only 13 months (type A, 15 months; type B, 12 months; type C, 13 months; $p < 0.001$). Two of 94 patients who did not undergo resection survived at least 5 years. One of them recently died of possible local tumor progression, with recurrent biliary obstruction and cholangitis. Both patients had pretreatment biopsies consistent with PA interpreted at MD Anderson by senior pathologists, but the absence of ex-

trapaneatic disease progression in both patients leaves room for continued debate over the diagnosis.

Among the 66 patients who completed all therapy including resection, recurrent pancreatic cancer developed, 39 (59%) patients; the median time to progression was 24 months. Forty-three sites of first recurrence were documented in 37 patients (the sites of first recurrence were unknown in 2 patients) and included distant organs (lung, liver, or bone) in 30 (45% of 66), the pancreatic bed in 6 (9% of 66), and regional sites (peritoneum or regional lymph nodes) in 7 (11% of 66). Isolated local recurrence was documented in 4 (6%) of the 66 patients who completed all therapy including surgery.

Factors associated with outcomes

Histologic assessment of tumor response to induction therapy was available in 63 of 66 patients. The 26 patients whose tumors demonstrated a minimal pathologic effect

from neoadjuvant therapy (treatment score IIa) had more than twice the risk of death as did the 37 patients with a partial or complete pathologic response to treatment (treatment score IIb, III, or IV; hazard ratio 2.74; 95% CI 1.27 to 5.89; $p = 0.01$). Although treatment effect was found to be notably associated with overall survival, the small number of patients makes it impossible to draw firm conclusions on the use of treatment effect as a surrogate marker for survival duration.

Evaluable CA19-9 levels at initial referral to MD Anderson Cancer Center were present in 105 (66%) of the 160 patients. We found no association between pretreatment serum CA 19-9 level and either the likelihood of undergoing pancreatectomy or overall survival. Both pretreatment and posttreatment (preoperative restaging) serum CA19-9 levels were available in 73 patients. To evaluate the association between the change in serum CA 19-9 levels over the course of therapy and outcomes, we divided these 73 patients into three groups: patients whose pretreatment CA 19-9 increased over the course of neoadjuvant therapy ($n = 16$); patients whose CA 19-9 decreased $\leq 50\%$ from pretreatment to posttreatment assessment ($n = 12$); and patients whose CA 19-9 level decreased $> 50\%$ from pretreatment to posttreatment assessment ($n = 45$). Compared with patients who had an increase in their serum CA 19-9 level over the course of neoadjuvant therapy, patients whose serum CA 19-9 fell were more likely to undergo pancreatectomy (odds ratio 4.2, 95% CI 0.8 to 21.0, $p = 0.08$ for patients with a $\leq 50\%$ fall in CA 19-9; odds ratio 5.4, 95% CI 1.5 to 19.7, $p = 0.01$ for patients whose CA 19-9 fell $> 50\%$). The percentage change in CA 19-9 over the course of neoadjuvant treatment was also associated with overall survival. Compared with patients who had a $> 50\%$ decrease in serum CA 19-9, patients with an increase in serum CA 19-9 had a greater than twofold risk of death (hazard ratio 2.4, 95% CI 1.2 to 4.9, $p = 0.02$).

Other factors considered in the prognostic factors evaluation included borderline type (A, B, or C) and lymph node status. No association between either of these potential covariates and overall survival was identified.

DISCUSSION

An important focus of clinical investigation by our multidisciplinary working group has been to accurately define the clinical stages of pancreatic cancer using objective, reproducible CT imaging criteria. This allows stage-specific therapy to be administered to patients of adequate performance status and is critical to the creation of reproducible eligibility criteria for clinical trials. In this report, we expand on our previously published definition of borderline resectable pancreatic cancer⁴ and offer a new, comprehen-

sive classification system for borderline resectable disease. We also report our initial institutional experience with the multidisciplinary management of borderline resectable patients, illustrating the favorable outcomes that can be achieved using a systematic, multidisciplinary approach in patients who might otherwise not be considered for potentially curative treatment.

Patients with resectable disease (stage I/II) have a normal tissue plane between the tumor and adjacent arterial structures and have a patent SMV-PV confluence. In contrast, patients with locally advanced disease (stage III) have tumor encasement (defined as $> 180^\circ$) of adjacent arteries or an occluded SMV-PV with no technical option for resection and reconstruction. Borderline resectable patients are those in the middle: tumor abutment ($\leq 180^\circ$) of adjacent arteries or an occluded SMV-PV confluence with an adequate segment of vein above and below the site of tumor involvement to allow for venous resection and reconstruction. In this report, we have expanded the definition of borderline resectable disease beyond patients with tumor-artery abutment (MD Anderson type A) to add those with questionable extrapancreatic metastatic disease (MD Anderson type B), and those with a marginal pretreatment performance status (MD Anderson type C). The type B and C subgroups arose out of observations made during our weekly multidisciplinary conferences in which we found that many patients were referred to us with physician uncertainty as to what clinical stage to assign for treatment planning (stage I/II versus stage IV in the type B patients), or with questions about which treatment should be considered in light of patient comorbidity and performance status issues (type C patients). We have seen these latter two subsets of borderline resectable patients—those with questionable metastatic disease (a group that may become more common as our imaging studies become more sensitive) and those with associated medical comorbidities or a performance status that makes up-front surgery of unacceptably high risk—with increasing frequency. It is our strong belief that this approach to pretreatment clinical staging allows for more accurate administration of stage-specific treatment, minimizes treatment indecision, and avoids unnecessary operations in patients who clearly have unresectable tumors. In addition, such a uniform staging system allows physicians to communicate with each other using a standard nomenclature for extent of disease and removes some of the imprecision from the terms *resectable* and *unresectable*.

A continued area of concern in the treatment of pancreatic cancer is that some patients may undergo laparotomy for planned pancreatic resection, but then not have resection because of local disease spread that could and should

have been appreciated on preoperative imaging. This failure to accurately perform or interpret CT images results in unnecessary laparotomy. The extent of this problem remains unknown and would, in fact, be difficult to quantify. In the referral-based population of borderline resectable patients reported here, 38 (24%) of 160 patients had undergone a nontherapeutic laparotomy before referral, including 18 (27%) of the 66 patients who ultimately underwent successful pancreatic resection at MD Anderson after neoadjuvant therapy. Local tumor extent can be accurately determined before operation, so patients should not be taken to the operating room for a planned pancreatectomy if the surgeon is not equipped to manage tumor-vessel involvement, which can almost always be detected on currently available cross-sectional imaging. In addition, there are no data to suggest that patients with locally advanced, stage III disease should undergo operation for attempted tumor resection. So, we consider neoadjuvant therapy and resectional surgery in cases of tumor-artery abutment (MD Anderson type A), but not arterial encasement (locally advanced, stage III). The data here strongly support this approach for two reasons. First, histologic complete responses were infrequent, suggesting that histologic response to induction therapy (to include radiation) is limited largely to a portion of the tumor, not all of it. So an incomplete gross resection (R2), which would result from attempted surgery in locally advanced stage III disease, is unlikely to provide clinical benefit even if preceded by induction therapy. Second, the histologic responses that were seen (histologic partial response in 37 [56%] of 66 patients) combined with the high rate of R0 resections (62 [83%] of 75 patients taken to surgery, and 62 [94%] of 66 patients who underwent resection) imply a clinically meaningful treatment response for at least the periphery of the tumor; it is unlikely that this would have occurred in the absence of induction therapy.

The oncologic outcomes observed in these patients with borderline resectable disease warrant comment. First, advanced nature borderline resectable pancreatic cancer is evidenced by the modest resectability rate seen in this group of patients; only 66 (41%) of 160 total patients had their tumors removed. When dealing with such complex surgery, which carries a risk of perioperative death (2 [3%] of 66 in this report), it is critically important to reserve operation for patients most likely to benefit. Second, giving neoadjuvant treatment allows selection for surgery of only those patients who are most likely to benefit and in whom the risks of major surgery can be justified. Indeed, in this study, the patients who completed all intended therapy, including resection of the pancreatic tumor, had a median survival of 40 months. In contrast, among patients who were considered poor candidates for surgery (owing mostly

to disease progression or poor performance status) at the time of posttreatment (preoperative) restaging, the median survival was only 13 months. These two distinct groups of patients cannot be differentiated at the time of diagnosis, but can be more accurately differentiated at the time of restaging, after 4 to 5 months of preoperative treatment—a distinct advantage of a treatment approach that places surgery after induction therapy. Our data illustrate that careful monitoring of borderline resectable patients as defined here, with attention to performance status, medical comorbidities, tolerance to therapy, serum levels of CA19-9, and serial CT imaging, will allow the multidisciplinary team to accurately determine which patients should be considered for a major abdominal operation.

The relatively small number of patients included in this report precludes a meaningful analysis of prognostic factors. For example, it is difficult to draw any firm conclusions on the use of histologic treatment effect as a surrogate marker for overall survival duration given the small sample size. Nonetheless, our data support assessment of treatment effect as a prognostic factor in future multimodality treatment studies. In addition, the effect of a prolonged course of neoadjuvant therapy likely accounted for the low frequency of lymph node-positive disease and the apparent modest effect of node-positive disease on survival. Ongoing research into molecular profiling of pancreatic cancer by us and others may provide additional or improved techniques to predict individual response to therapy. Now and in the future, the value of a multidisciplinary working group that reviews in detail all aspects of a patient's care during therapy cannot be overemphasized.

In summary, we have reported our recent experience with a newly described category (clinical stage) of patients with pancreatic cancer termed borderline resectable. The subgrouping of these patients into MD Anderson types A, B, and C, based on anatomic and patient factors, is particularly useful because doing so draws special attention to that aspect of the patient's case that is likely to be the limiting factor in achieving possible cure. We believe that our classification system adds more detail to the current AJCC staging system,¹² allowing all patients with pancreatic cancer to be accurately staged by clinical and radiologic criteria at the time of diagnosis. Last, this report defines a subgroup of patients about whom there is major confusion about stage assignment and treatment—namely, those whose tumors are not clearly resectable or clearly locally advanced. We hope that others will find this nomenclature useful in clinical practice and especially, for the design of clinical trials exploring nonsurgical therapies delivered pre- or postoperatively.

Author Contributions

Study conception and design: Katz, Pisters, Evans, Lee, Fleming, Crane, Wolff, Varadhachary, Hwang

Acquisition of data: Katz, Hwang

Analysis and interpretation of data: Katz, Pisters, Evans, Sun, Hwang

Drafting of manuscript: Katz, Pisters, Evans, Hwang

Critical revision: Fleming, Vauthey, Abdalla, Crane, Wolff, Varadhachary

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Discussion

DR MICHAEL A CHOTI (Baltimore, MD): The group from M.D. Anderson should be congratulated on their ongoing work both to characterize the criteria of resectability, identify this borderline subset group, and to emphasize the work on neoadjuvant therapy for this disease which certainly may be promising in the future. This paper really is a refinement of the “borderline resectable” situation described in the past. I have a comment and a few questions.

While I agree that it is important to define a subset of patients who may be best served by neoadjuvant therapy, I am not sure that lumping these three distinct definitions of “borderline resectability” really makes sense in this group. While the anatomically borderline patient certainly is important, and you have previously described that as well as you have here, the patients with this indeterminate liver lesion is really a matter of accurate staging in these patients, and similarly the patients with associated co-morbid disease I am not sure one can fairly classify that as a borderline resectable patient.

As I mentioned, the group C patients is not so much really a matter of the biology or differences in biology but just a matter of identifying whether these patients could tolerate the therapy, and the group B patients are really those that if you wait long enough you will see whether that indeterminate liver lesion is in fact positive or not. It is the anatomic group in which really the goal is to achieve perhaps a response and increase the R0 resection rate.

So the most important clinical question I think I have is regarding anatomically borderline resectable patients. Should we operate first on these patients, or really is neoadjuvant therapy the best strategy? It is hard to use this study to decide because all of these patients were treated with neoadjuvant therapy, and it is the sense that it increases the resectability rate, but your R0 resection rate is high, we have no comparison for this to show that, and even in your resectable patients, initially resectable, you report in the past comparable high R0 resection rates. Arguably, the radiologic response rates are really not dramatic in this group of patients. Are you actually improving the resectability, or are you just selecting patients who would go on to delaying patients, if you will, for these high-risk operations, which in itself may in fact be a useful reason for offering neoadjuvant therapy.

The second question relates to how you manage the preoperative chemoradiation therapy in these borderline patients. Unlike the true neoadjuvant therapy which has been reported by M.D. Anderson in the past where the duration of therapy is relatively short, here you present five to six months of adjuvant therapy, some patients receiving a few months, some receiving more than a year from the time of initial diagnosis to the time of surgery. How were the decisions made regarding when to operate and what was different among the three different groups regarding how one makes the decision when to pull the trigger, if you will?

Finally, based on these data can you speculate as to the role, if any, of attempting resection even in patients that are clearly unresectable? In your opinion, if one has a high grade of encasement, as you have shown, and let’s say a PET response or some response occurs, should we be actually considering, if ever, operating on these patients in the hopes of carving it off the vessel, if you will, and sterilizing the margin, if you will?