Margin Positive Pancreaticoduodenectomy Is Superior to Palliative Bypass in Locally Advanced Pancreatic Ductal Adenocarcinoma

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Abstract

Background Pancreatic ductal adenocarcinoma is an aggressive disease. Surgical resection with negative margins (R0) offers the only opportunity for cure. Patients who have advanced disease that limits the chance for R0 surgical resection may undergo margin positive (MP) pancreaticoduodenectomy (PD), palliative surgical bypass (PB), celiac plexus neurolysis alone (PX), or neoadjuvant chemoradiation therapy in anticipation of future resection.

Objective The aim of this study was to determine if there is a difference in the perioperative outcomes and survival patterns between patients who undergo MP PD and those who undergo PB for locally advanced disease in the treatment of pancreatic ductal adenocarcinoma.

Methods We reviewed our pancreatic surgery database (January 2005–December 2007) to identify all patients who underwent exploration with curative intent of pancreatic ductal adenocarcinoma of the head/neck/uncinate process of the pancreas. Four groups of patients were identified, R0 PD, MP PD, PB, and PX.

Results We identified 126 patients who underwent PD, PB, or PX. Fifty-six patients underwent R0 PD, 37 patients underwent MP PD, 24 patients underwent a PB procedure, and nine patients underwent PX. In the PB group, 58% underwent gastrojejunostomy (GJ) plus hepaticojejunostomy (HJ), 38% underwent GJ alone, and 4% underwent HJ alone. Of these PB patients, 25% had locally advanced disease and 75% had metastatic disease. All nine patients in the PX group had metastatic disease. The mean age, gender distribution, and preoperative comorbidities were similar between the groups. For the MP PD group, the distribution of positive margins on permanent section was 57% retroperitoneal soft tissue, 19% with more than one positive margin, 11% pancreatic neck, and 8% bile duct. The perioperative complication rates for the respective groups were R0 36%, MP 49%, PB 33%, and PX 22%. The 30-day perioperative mortality rate for the entire cohort was 2%, with all three of these deaths being in the R0 group. The median follow-up for the entire cohort was 14.4 months. Median survival for the respective groups was R0 27.2 months, MP 15.6 months, PB 6.5 months, and PX 5.4 months.

Conclusions Margin positive pancreaticoduodenectomy in highly selected patients can be performed safely, with low perioperative morbidity and mortality. Further investigation to determine the role of adjuvant treatment and longer-term follow-up are required to assess the durability of survival outcomes for patients undergoing MP PD resection.

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Introduction

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the USA. In 2008, there were an estimated 37,680 new cases diagnosed and 34,290 deaths. The overall 5-year survival rate is less than 5%.[1] Surgical resection of pancreatic adenocarcinoma is the only potentially curative therapy, and it improves the overall 5-year survival rate to 15–20%.[2,3] Unfortunately, most patients are not candidates for surgical resection at the time of diagnosis due to the presence of locally advanced disease, distant metastasis, or significant medical comorbidities.

Locally advanced pancreatic adenocarcinoma is generally defined by the presence of tumor abutment of the celiac trunk/superior mesenteric artery (SMA), or greater than 180° involvement/thrombosis of the superior mesenteric (SMV)/portal venous (PV) axis.[4–7] Preoperative evaluation of patients is in part designed to assess these anatomic factors and is successful in selecting appropriate candidates for resection 70–85% of the time.[8] High-quality contrast-enhanced multidetector computed tomography (CT) scan, magnetic resonance imaging (MRI), and endoscopic ultrasound examination are common diagnostic modalities used to determine tumor resectability. If unequivocal findings of locally advanced disease are encountered on preoperative imaging, patients are considered for neoadjuvant chemotherapy/radiation in an attempt to downstage the tumor. These patients, as well as those with distant disease, may also be candidates for palliative surgical management to alleviate tumor-related symptoms, such as gastrointestinal or biliary obstruction and refractory abdominal pain. In all, perhaps only up to 20% of patients at the time of diagnosis are eligible to undergo surgical resection, and recent evidence suggests that even this small group of potentially resectable patients is undertreated in the USA.[9,10]

Controversy remains as to the proper course of management when the patient with potentially resectable pancreatic adenocarcinoma is found in the operating room to have tumor approaching the hepatic artery (HA), SMA, or the SMV/PV axis. Intraoperative assessment in these cases is made challenging by the difficulty in distinguishing true tumor extension from peritumoral inflammation. In the past, palliative surgical bypass of the gastrointestinal and biliary tracts has been the standard course of therapy in many of these cases.[11] In recent years, with the improving safety of the Whipple procedure in many high volume centers, more of these tumors are being resected.[12,13] Proceeding with resection not only may result in complete disease removal (R0) but may also lead to microscopically positive (R1) or macroscopically positive (R2) resection margins. There are a number of factors that the surgeon must weigh before proceeding with this type of resection. Most important is safety, as the extensive dissection along the mesenteric vessels that is required to remove these tumors has the potential to cause visceral vessel injury and substantial blood loss. Other factors to consider are the potential benefit of tumor debulking upon the success of adjuvant treatment, the quality of life of the patient, and the effect of resection upon long-term survival. There is strong evidence to suggest that microscopically positive surgical margins are an important negative prognostic indicator and that the results of margin positive (MP; R1) resection are not equivalent to that of R0 resection.[14–18] However, the question remains as to how MP resection compares to palliative surgical bypass (PB) in borderline resectable disease. The objective of this study is to determine if there is a difference in the perioperative outcomes and survival patterns between patients who undergo margin positive pancreaticoduodenectomy (MP PD) and those who undergo palliative bypass for locally advanced disease in the treatment of pancreatic ductal adenocarcinoma.

Methods

We performed a retrospective review of our prospectively acquired hepatopancreatobiliary (HPB) surgery database in the Department of Surgery of Thomas Jefferson University. The database has been approved for data acquisition and query by our Institutional Review Board. Our database first began enrolling patients prospectively in January 2005, and we analyzed the data on consecutive patients explored for pancreatic ductal adenocarcinoma of the head, neck, or uncinate process of the pancreas over a 3-year period until December 2007. Four broad groups of patients were identified, those who underwent pancreaticoduodenectomy (both margin negative (R0) and MP patients were individually analyzed), those who underwent a palliative surgical bypass (including any combination of gastrointestinal or biliary bypass), and those who underwent celiac plexus neurolysis alone (PX). We analyzed patient demographics, preoperative comorbidities, operative techniques, intraoperative and postoperative variables and complications, postoperative hospital length of stay, and survival.

All of the patients included in this study underwent a standard preoperative evaluation that included a history and physical exam, standard laboratory evaluation along

with measurement of serum tumor markers (carcinoembryonic antigen (CEA) and cancer antigen (CA) 19–9), and some combination of high-quality contrast-enhanced cross-sectional imaging (CT or MRI). Many but not all patients had endoscopic ultrasound and/or endoscopic retrograde cholangiopancreatography. Patients were deemed potentially resectable and candidates for exploration if they lacked tumor involvement of the celiac axis/HA/SMA and had a patent SMV/PV with less than 180° tumor abutment and had no evidence of distant metastasis. Based upon this evaluation, patients were taken for operative exploration with the intent for a curative margin negative resection. All operations were performed at the Thomas Jefferson University Hospital by one of three experienced pancreatic surgeons (CJY, EPK, ELR).

Pancreaticoduodenectomy was performed with pylorus preservation whenever possible. The visceral vessels were routinely skeletonized, intentionally leaving no tissue behind along the SMV/PV or right lateral aspect of the SMA. A standard technique of end-to-side pancreaticojejunostomy and hepaticojejunostomy (HJ) with downstream retrocolic duodenojejunostomy was used, as has been previously described.[19] Patients were considered intraoperatively for palliative surgical bypass if they were found on exploration to have occult metastatic disease (and had evidence of impending gastrointestinal or biliary obstruction) or if their tumor was deemed locally advanced preventing an attempt at margin negative resection. The technique for gastrointestinal bypass was most commonly a two-layered hand-sewn side-to-side retrocolic isoperistaltic gastrojejunostomy (GJ). Biliary bypass was typically performed as a single-layer end-to-side Roux-en-Y hepaticojejunostomy. Celiac plexus neurolysis (nerve block) was performed by using a total volume of 40 ml of 50% ethanol, injecting 20 ml of the solution on either side of the aorta, at the level of the celiac axis. All patients with occult metastasis discovered at the time of surgery underwent celiac plexus neurolysis. Variable numbers of patients in the PD and PB groups underwent this procedure based upon patient factors such as preoperative pain, as well as surgeon preference. There was incomplete data on the number of R2 resections in the MP group, and therefore, this was not included in the results. Resected specimens underwent histopathologic evaluation for tumor size, histologic grade, lymph node involvement, lymphovascular invasion, perineural invasion, and resection margin status. Disease was staged according to the American Joint Committee on Cancer (AJCC) guidelines and meticulously reported per the College of American Pathologists guidelines.[20,21] Bile duct, pancreatic neck, and retroperitoneal soft tissue (uncinate) margins were routinely evaluated intraoperatively by frozen section analysis and were further assessed postoperatively on permanent examination of inked margins. R0 resections were considered those that lacked tumor involvement of the inked margins, whereas R1 resections had microscopically positive margins on the specimen side of the resection specimen.

Data collection was performed using information within our clinical HPB database and supplemented by reviewing patient charts and computer records. Demographic data were acquired on patient age, gender, race, social history, and body mass index (BMI). Preoperative comorbidities such as coronary artery disease, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, cerebrovascular disease, peripheral vascular disease, and pancreatitis were evaluated. Operative variables such as estimated blood loss, transfusion requirement, and type of resection (classic Whipple vs pylorus preserving) were acquired. Postoperative complications were examined including wound infection, myocardial infarction, arrhythmia, venous thrombosis, pulmonary embolism, pneumonia, urinary tract infection, pancreatic fistula, and delayed gastric emptying, among others. Complications were graded using a system adapted from DeOliveira et al.[22] Pancreatic fistula was defined and graded by a system adapted from the International Study Group on Pancreatic Fistula (ISGPF).[23] Postoperative hospital length of stay and 30-day mortality were recorded. Hospital readmission rates included admission to the Thomas Jefferson University Hospital as well as to outside facilities. Survival was determined using time of last clinical follow-up, direct communication with patients and families, and the Social Security Database.

Statistical Methods

Demographic and clinical characteristics were summarized using means, medians, and ranges (continuous outcomes) and frequencies and percentages (categorical outcomes). Groups were compared using Wilcoxon rank-sum tests for continuous outcomes and Fisher's exact test for categorical outcomes. Survival distributions were estimated using the Kaplan–Meier method and groups were compared using the log-rank test. In addition, Cox proportional hazards regression was used to estimate the hazard ratio between groups, after adjusting for potential confounders. A propensity score model was used to adjust for factors associated with choice of procedure (age, diabetes, preoperative blood urea nitrogen, and COPD). A logistic regression model was used to calculate the probability of having a procedure given a particular preoperative profile, and this probability was
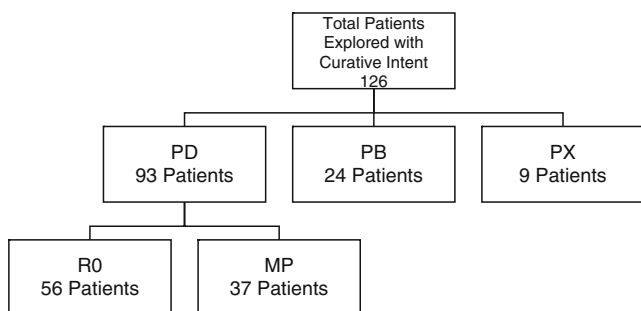
Figure 1 Patients explored with curative intent. *R0* margin negative pancreaticoduodenal resection, *MP* margin positive pancreaticoduodenal resection, *PB* palliative bypass, *PX* celiac plexus neurolysis, *PD* pancreaticoduodenectomy.

then included as a covariate in the proportional hazards model. Adjusted and unadjusted estimates of the geometric mean ratio for estimated blood loss and length of stay were calculated using linear regression. Logistic regression was used to estimate unadjusted and adjusted odds ratios for the presence of postoperative complications. Significance was accepted at the $p<0.05$ level.

Results

Demographics and Preoperative Characteristics

During the 3-year study period January 2005–December 2007, we identified 126 patients with pathologically confirmed pancreatic ductal adenocarcinoma that underwent surgical exploration with curative intent (Fig. 1). Of this cohort, 93 patients underwent pancreaticoduodenectomy; 56 of these patients had margin negative resections (R0), while 37 of these patients had margin positive resections. Twenty-four patients were deemed unresectable due to metastatic disease ($N=18$) or local tumor extension ($N=6$) and underwent a palliative surgical bypass procedure. Nine patients were found to have metastatic disease without indication for bypass and underwent celiac plexus neurolysis alone. The male/female ratio of the entire cohort was 48:52%, and the median age was 64 years (Table 1). The median preoperative serum albumin level was 4.0 g/dl and was similar between groups. Patients in the PB and PX groups had higher preoperative median CA 19–9 and CEA levels

Table 1 Demographics and Preoperative Variables

	Total n (%)	R0	MP	p value (R0 vs MP)	PB	p value (MP vs PB)	PX
Total, n	126 (100)	56	37		24		9
Gender, n (%)							
Male	61 (48)	28 (50)	19 (51)	NS	12 (50)	NS	2 (22)
Female	65 (52)	28 (50)	18 (49)	NS	12 (50)	NS	7 (78)
Age (years)							
Median	64	64.5	65	NS	62	NS	67
Range	35–86	41–84	35–86	–	43–80	–	51–81
Albumin (g/dl)							
Median	4.0	4.2	3.9	NS	4.0	NS	4.0
Range	2.0–5.5	2.3–5.1	2.0–5.0	–	2.6–5.5	–	3.3–4.3
CA 19–9 (U/ml)							
Median	284	167	259	NS	642	NS	852.5
Range	2–80,809	2–6,994	3–80,809	–	2–11,655	–	74–9,348
CEA (ng/ml)							
Median	2.9	2.4	2.7	NS	3.5	NS	5.45
Range	0.5–161.1	0.9–29.8	0.8–81.2	–	0.5–17.1	–	0.9–161.1
Preoperative comorbidities, n (%)	77 (61.0)	28 (50.0)	28 (75.6)	<0.0174	16 (66.6)	<0.0014	5 (55.5)
DM	48 (38.1)	25 (44.6)	15 (40.5)	NS	5 (20.8)	NS	3 (33.3)
Tobacco	41 (32.5)	21 (37.5)	9 (24.3)	NS	9 (37.5)	NS	2 (22.2)
BMI							
Median	25	25	25	NS	25	NS	32
Range	15–41	15–41	18–36	–	15–38	–	20–37

R0 margin negative pancreaticoduodenal resection, *MP* margin positive pancreaticoduodenal resection, *PB* palliative bypass, *PX* celiac plexus neurolysis, *BMI* body mass index, *DM* diabetes mellitus

Table 2 Perioperative Variables

	Total n (%)	R0	MP	p value (R0 vs MP)	PB	p value (MP vs PB)	PX
Total	126 (100)	56	37		24		9
Type of procedure							
PPPD	63 (50.0)	40 (71.4)	23 (62.2)	NS	–	–	–
Classic Whipple	30 (23.8)	16 (28.6)	14 (37.8)	NS	–	–	–
GJ + HJ	14 (11.1)	–	–	–	14 (58.3)	–	–
Gastrojejunostomy alone	9 (7.1)	–	–	–	9 (37.5)	–	–
Hepaticojejunostomy alone	1 (0.8)	–	–	–	1 (4.1)	–	–
Celiac plexus neurolysis	34 (27.0)	2 (3.6)	1 (2.7)	NS	22 (91.6)	<0.0001	9 (100)
EBL (ml)							
Median	500.0	650.0	600.0	NS	200.0	<0.0001	100.0
Range	75–1,800	200–1,500	800–1,800	–	75–500	–	100–250
Complications, n (%)	48 (38.1)	20 (35.7)	18 (48.6)	NS	8 (33.3)	NS	2 (22.2)
Wound infection	16 (12.7)	6 (10.7)	7 (18.9)	NS	2 (8.3)	NS	1 (11.1)
Cardiac	12 (9.5)	7 (12.5)	4 (10.8)	NS	1 (4.2)	NS	0 (0)
P. fistula	7 (7.5[a])	5 (8.9)	2 (5.4)	NS	0 (0)	NS	0 (0)
DGE	5 (4.0)	1 (1.8)	3 (8.1)	NS	1 (4.2)	NS	0 (0)
Abdominal abscess	5 (4.0)	2 (3.6)	2 (5.4)	NS	1 (4.2)	NS	0 (0)
UTI	5 (4.0)	1 (1.8)	2 (5.4)	NS	1 (4.2)	NS	1 (11.1)
C. diff. colitis	3 (2.4)	0 (0)	1 (2.7)	NS	1 (4.2)	NS	1 (11.1)
Chyle leak	3 (2.4)	0 (0)	3 (8.1)	NS	0 (0)	NS	0 (0)
DVT	3 (2.4)	1 (1.8)	0 (0)	NS	1 (4.2)	NS	1 (11.1)
Length of stay (days)							
Median	7	7	7	NS	5.5	<0.0009	5
Range	3–25	3–25	5–19	–	3–13	–	4–24
Readmissions, n (%)	25 (19.8)	14 (25.0)	9 (24.3)	NS	2 (8.3)	NS	0 (0)

R0 margin negative pancreaticoduodenal resection, *MP* margin positive pancreaticoduodenal resection, *PB* palliative bypass, *PX* celiac plexus neurolysis, *PPPD* pylorus preserving pancreaticoduodenectomy, *EBL* estimated blood loss, *DGE* delayed gastric emptying, *P. fistula* pancreatic fistula, *UTI* urinary tract infection, *C. diff. colitis* clostridium difficile colitis, *DVT* deep venous thrombosis

[a] Calculated based on pancreaticoduodenectomy patients only

than either the R0 or MP groups. Preoperative comorbidities were observed in 61% of all the patients and in the respective groups were R0 50%, MP 76%, PB 67%, and PX 56%. The PX group had a higher median BMI (32) than the other groups (25). Five of the patients in the series received neoadjuvant chemoradiation therapy. Of these patients, four underwent R0 resection and one underwent a MP resection.

Operative Management

Of the 93 pancreaticoduodenectomies performed in this series, 63 were pylorus preserving and 30 were classic Whipple resections (Table 2). Two patients in the series underwent portal venous resection and reconstruction. Of the 24 patients who underwent palliative surgical bypass, 58% underwent GJ plus HJ, 38% underwent GJ alone, 4% underwent HJ alone, and 92% of these patients received a concomitant celiac plexus block. Of these 24 PB patients, 25% underwent

Table 3 Modified Clavien Classification of In-hospital Postoperative Surgical Complications

	R0, n (%)	MP, n (%)	PB, n (%)
Total patients	56	37	24
Complications			
Total	20 (35.7)	18 (48.6)	8 (33.3)
Type I	4 (7.1)	3 (8.1)	0 (0)
Type II	10 (17.9)	10 (27.0)	5 (20.8)
Type IIIa/b	5 (8.9)	5 (13.5)	2 (8.3)
Type IVa/b	0 (0)	0 (0)	1 (4.1)
Type V	1 (1.8)	0 (0)	0 (0)

Adapted from DeOliveira et al.[22]

Grade I any deviation from normal postoperative course without pharmacological/surgical treatment, *Grade II* requiring pharmacological treatment with drugs, *Grade III* requiring surgical/radiological/ endoscopic intervention, *Grade IV* life-threatening complication requiring ICU management, *Grade V* death of patient, *R0* margin negative pancreaticoduodenal resection, *MP* margin positive pancreaticoduodenal resection, *PB* palliative bypass

Table 4 Pathology in Resected Patients

	Total PD, n (%)	R0, n (%)	MP, n (%)	p value (R0 vs MP)
Total, n	93	56	37	
T stage[20]				
T1	9 (9.7)	7 (12.5)	2 (5.4)	NS
T2	23 (24.7)	19 (33.9)	4 (10.8)	<0.05
T3	61 (65.5)	30 (53.5)	31 (83.7)	<0.05
T4	0 (0)	0 (0)	0 (0)	–
Differentiation				
Poor	15 (16.1)	10 (17.9)	5 (13.5)	NS
Moderate	71 (76.3)	40 (71.4)	31 (83.7)	NS
Well	7 (7.5)	6 (10.7)	1 (2.7)	NS
Lymph nodes				
Positive nodes, n (%)	61 (65.6)	32 (57.1)	29 (78.4)	<0.05
Resected median (mean)	12 (13.2)	11 (12.6)	14 (14.0)	NS
Positive median (mean)	1 (2.8)	1 (1.8)	4 (4.3)	<0.05
(+) Lymphovascular invasion	34 (36.6)	16 (28.6)	18 (48.6)	NS
(+) Perineural invasion	77 (82.8)	43 (76.8)	34 (91.8)	NS

R0 margin negative pancreaticoduodenal resection, *MP* margin positive pancreaticoduodenal resection, *PB* palliative bypass, *PD* pancreaticoduodenectomy

the procedure for borderline resectable or locally advanced disease and 75% for metastatic disease. Celiac plexus neurolysis alone was performed in nine patients, and in each such case, the patient was well palliated by a biliary endoprosthesis and there was no impending tumor encroachment on the duodenum, reflecting the lack of need for gastrojejunostomy. All patients in the PX group had metastatic disease. Median estimated blood loss for the entire cohort was 500 ml and was higher in the R0 and MP groups (650 and 600 ml, respectively) than it was in the PB and PX groups (200 and 100 ml, respectively; *p*<0.05).

Perioperative Morbidity and Mortality

The postoperative morbidity rate for the entire cohort was 38% (Table 2), reflecting differing rates per group: R0 36%, MP 49%, PB 33%, and PX 22%. The most common complications identified were wound infection 13%, cardiac 10%, pancreatic fistula 8%, delayed gastric emptying 4%, intraabdominal abscess 4%, urinary tract infection 4%, pneumonia/pleural effusion 3%, Clostridium difficile infection 2%, chyle leak 2%, and deep venous thrombosis 2%. The pancreatic fistula rate in the R0 group was 9% and in the MP group was 5%. Of these pancreatic fistulae, 43% were type A, and 57% were type B, as defined by the ISGPF. There were no type C pancreatic fistulae. Median postoperative length of hospital stay was 7 (5–25) days for patients undergoing pancreaticoduodenectomy (R0 and MP) and 5 (3–24) days for patients undergoing PB or PX (*p*<0.05). The readmission rate to either Thomas Jefferson University Hospital or outside hospitals for the entire cohort was 20%, 25% for patients undergoing pancreaticoduodenectomy, and 8% for those undergoing PB. The 30-day perioperative

mortality for the entire cohort was 2%. All three of these deaths were in the R0 group (5%). Two of these patients died suddenly at home 6 and 3 days after discharge, having been progressing well both in-hospital and at home. The cause of death was not clear in either case, and they were suspected to be due to pulmonary embolus or cardiac arrhythmia. The third patient died in the hospital on postoperative day 3 when he became bradycardic and hypotensive following an episode of massive emesis with aspiration.

Table 3 shows complications classified by a system adapted from DeOliveira et al.,[22] comparing the R0, MP, and PB groups. All three groups had similar rates of high-grade types III and IV complications, while the MP group had the highest rate of type II complications.

Pathology and Surgical Margins

Of the patients who underwent surgical resection of their tumors, the patients with MP resections had significantly

Table 5 Location of Positive Margins in MP Patients (*n*=37)

Positive margin	No. of patients (%)
Retroperitoneal soft tissue	21 (57)
More than 1 positive margin	7 (19)
Pancreatic neck	4 (11)
Bile duct	3 (8)
Circumferential	2 (5)

Retroperitoneal soft tissue represents the pancreatic soft tissue adjacent to the SMV/PV ventrally and the SMA dorsally. Circumferential = soft tissue that lies dorsal to the pancreatic head and uncinate which is bounded by the inferior vena cava, aorta, and left renal vein

Table 6 Survival

	Total (n=126)	R0 (n=56)	MP (n=37)	p value (R0 vs MP)	PB (n=24)	p value (MP vs PB)	PX (n=9)
Median survival (months)	14.8	27.2	15.6	NS	6.5	<0.05	5.4
1-year survival (%)	58.7	71.5	64.9	NS	29.2	<0.05	12.5

R0 margin negative pancreaticoduodenal resection, *MP* margin positive pancreaticoduodenal resection, *PB* palliative bypass, *PX* celiac plexus neurolysis

higher percentages of T3 tumors (84% vs 54%, $p<0.05$) and lymph node involvement (78% vs 51%, $p<0.05$) and higher rates of perineural and lymphovascular invasion as compared to the R0 patients (Table 4). For the MP group, the distribution of positive margins on permanent section (Table 5) was 57% retroperitoneal soft tissue (uncinate), 19% with more than one positive margin, 11% pancreatic neck, 8% bile duct, and 5% circumferential. Of the patients with more than one positive margin, the retroperitoneal soft tissue (uncinate) was involved 86% of the time.

Survival

The median follow-up period for the entire cohort was 14.4 months. The median survival times estimated from the Kaplan–Meier curves for the respective groups were 27.2 months for the R0 group, 15.6 months for the MP group, 6.5 months for the PB group, and 5.4 months for the PX group (Table 6; Fig. 2). One-year survival rates for the groups were R0 72%, MP 65%, PB 29%, and PX

13%. When comparing the MP group with the subgroup of PB patients with locally advanced disease (PB-L; $N=6$), the median survival times were 15.6 vs 13.2 months, and the 1-year survival rates were 65% vs 50%, respectively (Table 7).

Although multivariate regression analysis did not reveal many statistically significant differences (Table 8), as would be expected, patients with smaller tumors (hazard ratio (HR), 0.78; 95% confidence interval (CI), 0.28–2.17; $p=0.63$) and those who underwent R0 resection (HR, 0.91; 95% CI, 0.50–1.68; $p=0.76$) tended to have longer survival. Patients who had positive resected lymph nodes (HR, 1.30; 95% CI, 0.59–2.87; $p=0.51$), perineural invasion (HR, 2.30; 95% CI, 0.96–5.50; $p=0.06$), and lymphovascular invasion (HR, 1.70; 95% CI, 0.92–3.14; $p=0.09$) tended to survive for shorter periods of time than if those factors were absent. Patients who underwent PB had a significantly increased likelihood of death as compared to those that underwent MP resection (HR, 2.52; 95% CI, 1.37–4.65; $p=0.003$). Additionally, for the subset of patients who underwent PB-L as compared to MP resec-

Figure 2 Kaplan–Meier survival curves for the four groups. For the R0 pancreatico-duodenectomy group, the median survival was 27.2 months, and the 1- and 2-year survival rates were 71.5% and 50.4%, respectively. For the MP pancreaticoduodenectomy group, the median survival was 15.6 months, and the 1- and 2-year survival rates were 64.9% and 32.9%, respectively. For the PB group, the median survival was 6.5 months, and the 1- and 2-year survival rates were 29.2% and 8.3%, respectively. For the PX group, the median survival was 5.4 months, and the 1- and 2-year survival rates were both 12.5%.
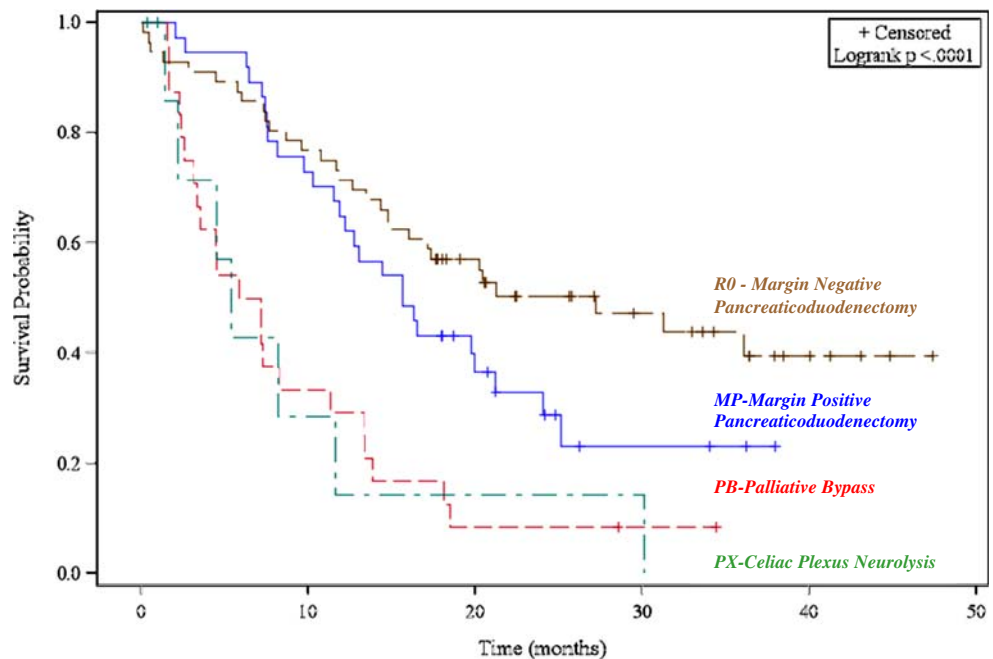
Table 7 MP vs PB Local Disease Survival

Survival	MP (n=37)	PB local disease (n=6)	p value
1 year (%)	64.9	50.0	0.65
2 years (%)	32.9	16.7	0.53
3 years (%)	23.0	–	–
Median (months)	15.6	13.2	0.4736

MP margin positive pancreaticoduodenal resection, *PB* palliative bypass

tion, there was a trend toward shorter survival (HR, 1.62; 95% CI, 0.64–4.13; p=0.31).

Discussion

Although careful preoperative evaluation of patients with pancreatic adenocarcinoma is designed to identify candidates for whom R0 resection is possible, during operative exploration, one is often confronted with a tumor that appears more advanced than previously thought. In some circumstances, this is because time has elapsed between high-quality CT or MR imaging and exploration, and in other cases, the imaging may have underrepresented the proximity of the tumor to the major visceral vessels. In such instances, the surgeon must decide whether to perform a resection with the possibility of microscopically positive margins or to leave the tumor in place and perform a palliative surgical bypass. The factors that the surgeon must consider in performing such a resection include safety, as well as the effects of tumor debulking upon adjuvant treatment, quality of life, and long-term survival. In this retrospective review of patients undergoing exploration with curative intent, we sought to compare the outcomes of patients undergoing MP resection with those who underwent PB for locally advanced disease in the treatment of pancreatic ductal adenocarcinoma.

In this study, we found that of the patients explored for pancreatic adenocarcinoma, 74% ultimately underwent pancreaticoduodenectomy. Of these, 39.8% were classified with careful pathologic assessment as margin positive resections, which falls within the range (14–60%) reported in the literature.[15,24] In the MP group, the most common site of margin positivity was the retroperitoneal soft tissue

(uncinate) margin, representing 73% of all of the margin positive cases. These findings are consistent with results reported in previous studies[25] and are not surprising, as this margin is typically the most difficult to clear. It represents the pancreatic soft tissue adjacent to the superior mesenteric vein and portal vein ventrally and the superior mesenteric artery dorsally. In our hands, every effort is made to resect this tissue from the right lateral aspect of the superior mesenteric artery during the initial separation of the specimen from the visceral vessels. Thus, further resection in this area for a positive margin is not typically possible without performing an arterial resection.

The data from our study suggest that margin positive pancreaticoduodenectomy can be performed safely, with low perioperative morbidity and mortality. The postoperative complication rates were similar between the R0 and MP groups, 36% and 49%, respectively, and were only slightly higher than in the PB group, 33%. Patients in the MP group tended to have a higher rate of minor Clavien types I and II complications when compared to the PB group (especially wound infections, 19% vs 8%), while more serious types III and IV complications were equally distributed between groups. The median postoperative length of hospital stay showed only a 1.5-day difference between patients undergoing resection (R0, MP 7 days) and those undergoing palliative bypass (5.5 days). This is likely because a traditional palliative double bypass, which includes a Roux-en Y hepaticojejunostomy as well as a gastrojejunostomy, involves three separate anastomoses and, aside from the risk of pancreatic fistula, has a similar complication profile to pancreaticoduodenectomy. Perioperative mortality for the entire cohort was only 2% and was confined to the R0 group. There was no perioperative mortality in the MP or PB groups.

Table 8 Multivariate Regression Analysis: Factors Affecting Survival

Parameter	Hazard ratio	95% Hazard ratio confidence limits		p value
R0 vs MP	0.910	0.495	1.675	0.7629
Stage (I vs II)	0.779	0.279	2.173	0.6332
Positive lymph nodes (>0 vs 0)	1.302	0.590	2.871	0.5135
Perineural invasion (yes vs no)	2.298	0.961	5.500	0.0615
Lymphovascular invasion (yes vs no)	1.704	0.924	3.144	0.0881
PB vs MP	2.521	1.366	4.653	0.0031
PB local vs MP	1.624	0.639	4.128	0.3083

R0 margin negative pancreaticoduodenal resection, *MP* margin positive pancreaticoduodenal resection, *PB* palliative bypass, *PB local* palliative bypass locally advanced disease

Some recent published reports have suggested that margin status does not independently affect disease recurrence or survival.[26,27] There are several theories that attempt to explain this finding. First, many patients will harbor silent local or distant metastases at the time of surgery, making the status of surgical resection margins less important than might generally be considered. This would explain the high rates of recurrence even in patients with disease thought to be completely resected. Secondly, because margin positivity is defined by the presence of microscopic tumor cells present on the specimen side of the margin, one might expect that a certain percentage of margin positive patients do not harbor further disease on the retained side, allowing their outcomes to more closely approximate the R0 group. Despite these theories, our data show the expected trend toward increased survival in R0 patients compared to MP patients, with 1-year survival (72% vs 65%) and median survival (27.2 vs 15.6 months) both favoring the R0 group, though these results did not reach significance. As would be expected, patients with MP resections had larger tumors and higher rates of lymph node involvement and lymphovascular and perineural invasion as compared to the R0 group.

A number of authors have suggested a role for margin positive resection by demonstrating that margin positive pancreaticoduodenectomy is associated with better survival than palliative bypass procedures.[28–30] In a recent study performed in the Royal Free and University College Medical School, median survival was significantly longer after MP resection than after PB (18 vs 9 months).[24] Our data are similar to this with 1-year survival rates between the groups of 65% and 29% and median survival of 15.6 and 6.5 months in the MP and PB groups, respectively. When looking at the subgroup of PB-L, patients who most closely approximate the MP group, there is a trend toward increased median survival in the MP group in absolute terms, though given the small sample size of the PB-L group, this difference was not significant. One-, 2-, and 3-year survival rates in the MP group were higher than in the PB-L group at 65% vs 50%, 33% vs 17%, and 23% vs 0%, respectively. The presence of a small number of long-term survivors in the MP group that we have found in this study is consistently identifiable in a number of major surgical series. This MP survival percentage tends to be fairly consistent between series and approximates 20% survival at 3 years.[24,27,31] The same cannot be said in examining series on PB, where the median survival length tends to be short (6 to 9 months) and 3-year survival rates approach 0–1%.[32–36] Although our sample size was too limited to reach statistical significance, the trends demonstrate that patients in the MP group behave more like the R0 group than the PB-L group. This suggests that in intraoperative decision making in a highly selected group

of patients, it would be reasonable to lean more toward resection than bypass.

The limitations of this study must be acknowledged. It used a retrospective design and had a relatively short follow-up period, and there were insufficient numbers to reach statistical significance for many of the identifiable trends. Moreover, there was incomplete data on adjuvant treatment which has been shown to impact survival[37] although not nearly to the extent as resection. Also, this study does not specifically deal with the issue of attempted resection for tumors that approach the visceral vessels vs delaying surgery in favor of neoadjuvant treatment. Furthermore, this study lacks quality of life assessment in the groups, an important aspect of pancreatic cancer therapy, decision making, and outcomes.

Conclusions

Margin positive pancreaticoduodenectomy for pancreatic ductal adenocarcinoma in a highly selected group of patients can be performed safely with low perioperative morbidity and mortality. Patients who undergo MP resection have outcomes more closely aligned with patients undergoing R0 resection as compared to patients undergoing PB for locally advanced disease. A small group of long-term survivors exist in the MP group that are not present in the PB for locally advanced disease group. Further work to determine the role of adjuvant treatment and longer-term follow-up are required to assess the durability of survival outcomes for patients undergoing MP resection.

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Discussant

Dr. Attila Nakeeb (Indianapolis, IN): Clearly your group has again shown that achieving an R0 resection margin is the most important factor in the management of pancreatic cancer. I have got a couple of questions regarding your philosophy and strategy in regards to these patients.

When you compare the palliative bypass group to the patients undergoing positive margin resection, almost 75% of your palliative bypass patients actually were bypassed in the setting of metastatic disease and not for locally advanced disease. I would like to get a feeling for your thoughts of whether surgical bypass and palliation are actually necessary in patients with metastatic disease. Do you employ any additional staging such as laparoscopy in patients with suspected metastatic disease, especially in patients with elevated CA 19–9 levels, because those have a much higher incidence of requiring palliative bypass.

Secondly, what is your approach to patients with borderline resectable tumors at Jefferson? Are those patients being taken to the operating room immediately with the plan for venous resection, or are they all going for neoadjuvant therapy?

Finally, in those patients that are not able to have an R0 resection, if you compare your margin positive Whipples to the palliative bypass patients, is there any difference in the number of patients that actually receive adjuvant therapy postoperatively or in the time it takes to start therapy?

Closing Discussant

Dr. Harish Lavu (Philadelphia, PA): Your first question asked about whether or not we routinely perform diagnostic laparoscopy given the high percentage of patients with metastatic disease. The answer is that in the majority of patients, we do not. We rely heavily on the CAT scan to help us differentiate these patients, and what we have found is that the majority of unresectable patients ultimately require some sort of palliative bypass, whether it be to the biliary tree or the gastrointestinal tract. We generally believe palliative bypass to be superior to endoscopic management in terms of quality of life in those patients who undergo exploration, so we do not routinely perform laparoscopy.

Your second question was regarding patients with borderline resectable disease, and how we select patients for neoadjuvant treatment? Patients who have superior mesenteric vein or portal vein occlusion or who have a greater than 180° encasement of these vessels with significant stenosis of the vein, or patients who have superior mesenteric artery or celiac axis abutment of tumor. Those are the kinds of patients that we routinely send for neoadjuvant treatment.

Your third question on adjuvant treatment, unfortunately I cannot answer. Many of our patients do not receive their adjuvant treatment at our facility and so it is difficult for us to get a good handle on who was receiving treatment and who was not and when.

Discussant

Dr. L. William Traverso (Seattle, WA): I would like to congratulate the Thomas Jefferson group—with the plethora of great research coming out of Philadelphia on this disease. We look forward to many more contributions.

I am trying to think now not as a surgeon but as a medical oncologist. I note that the 13 months in survival time for the nonresected group outstrips that of the literature, which is about 9 months. You have already made progress there. In Seattle, it is 18 months for the nonresected group, higher than your margin positive Whipple group. Part of this may be experience to choose which chemotherapy will allow a response so it is no longer as much empiric but targeted therapy, somewhat.

I wonder if you might consider the following study—a patient totally managed endoscopically with stents, screened with prechemo laparoscopy (the latter will removed 28% of the patients as they will have positive peritoneal cytology), and then targeted therapy. Therefore, you have the perfect group to compare to the margin positive resected group. I expect in the next 5 years that we will observe 3- or 4-year survivors without any surgery, as we have seen in Seattle. Would you consider that study?

Closing Discussant

Dr. Harish Lavu (Philadelphia, PA): I think we would consider that. It is a very interesting point that you bring up. I would say that there are a number of studies now that are questioning the difference in outcomes between R0 resection and margin positive resections, specifically R1 resections, in terms of how it affects survival and to what time frame does it affect survival?

We know that surgical resection is superior to any adjuvant treatment that is commonly used today. So I think that if there are breakthroughs in adjuvant treatment in the future, there may develop a more aggressive philosophy toward taking patients for surgical resection.