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Postoperative complications and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma

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Abstract

INTRODUCTION—Pancreaticoduodenectomy (PD) performed for pancreatic ductal adenocarcinoma (PDA) has a postoperative morbidity of 40–50%. In this study, we analyzed the impact of high grade complications after PD for PDA on overall survival.

METHODS—596 patients that underwent PD for PDA between 2001–2009 were identified from a prospective database. Complications were defined and graded (1–5) as per our Institutional Surgical Secondary Events Program. High grade complications were defined as grade 3. Postoperative mortality (90 days) was excluded. Univariate and multivariate analyses were performed to identify factors associated with overall survival.

RESULTS—Median survival was 24 months. Overall complication rate was 51% (301/596). Low grade complications were recorded in 266 patients (45%) and high grade complications in 22% (n= 129). Our 90 day mortality was 3.7% (n= 22). Anastomotic fistula/ leak/abscess rate was 14% (n= 82). Multivariate Cox-Regression analysis identified node positivity, estimated blood loss (EBL) > 600 ml, length of stay (LOS) > 10 days, margin positivity and vascular procedures as predictors of decreased overall survival ($p < 0.05$). High grade complications were not associated with overall survival ($p = 0.948$).

CONCLUSION—In this study, the occurrence of high grade postoperative complications was not associated with overall survival.

Keywords

Pancreaticoduodenectomy; pancreatic ductal adenocarcinoma; survival; complications

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INTRODUCTION

Pancreaticoduodenectomy (PD) is the standard procedure performed for pancreatic ductal adenocarcinoma (PDA) arising in the peri-ampullary region of the pancreas. PD is regarded as a complex operation with perioperative morbidity rates ranging from 40% – 58% [1–4]. The perioperative mortality rate for PD from the initial series of 41 patients reported by Whipple in 1941 was 29% [5]. Careful patient selection, improvements in surgical technique, and improvements in perioperative care has reduced this mortality rate to 2–4% in high volume centers [6–8]. Despite the improvement in operative mortality, the overall five year survival for patients who have undergone resection for PDA remains between 5% and 10% [9].

Currently, surgical resection is the standard treatment for resectable pancreatic cancer and patients who undergo resection typically experience median survival rates of 20–24 months [10–12]. Identifying modifiable factors that are associated with survival outcome is a major focus of research in surgical oncology. A study analyzing the National Surgical Quality Improvement Program Data identified a negative association between postoperative morbidity and survival following selected major operations [13]. Similarly, postoperative morbidity was associated with long-term outcome after procedures for several different malignant diseases, including colorectal cancer [14–16], head and neck cancer [17] and esophageal cancer [18]. However, the influence of post-operative morbidity after PD for PDA on overall survival is still unclear. In this study, we evaluated if clinically significant postoperative complications (grade 3, Table 1), after PD for PDA were associated with overall survival.

METHODS

Memorial Sloan Kettering Cancer Center's (MSKCC) Institutional Review Board approval was obtained before commencing this study. Our prospectively maintained pancreatic database was queried for patients who underwent PD for PDA. We identified 596 patients who underwent PD from January 2000 to December 2009. We excluded patients who underwent PD for other histologic subtypes.

Preoperative, intraoperative, and postoperative variables, along with survival data and disease status of patients were retrieved and analyzed from electronic medical records and follow up from physicians. Postoperative complications were graded in severity using a scale of 1 to 5 as per the MSKCC Secondary Surgical Events Program, as previously described [19]. High grade complications were defined as grade 3 (see Table 1 for example of definition and grading schema). We do not routinely use postoperative drains, nor do we routinely measure drain amylase when they are put in at the time of operation. The presence of bile in the drain was what was utilized to define biliary leak. Specific imaging or interventional procedures were not routinely used to define type of leak. Negative margins are those free of tumor cells 1 mm away from surgical margin. All events recorded within 90 days of resection were considered to be postoperative complications. Patients underwent either a standard Whipple procedure or a pylorus preserving PD with or without additional vascular resections as required.

Clinicopathologic variables evaluated included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, preoperative albumin, operative time, additional procedures (vascular repair or resection), estimated blood loss (EBL), pathological margin status, T stage, nodal status, postoperative complications, length of stay (LOS) and overall survival. All tumors were staged based on the seventh edition of the American Joint Committee on Cancer Staging. There are no stage 4 patients or stage 3 patients in the study group. Death occurring > 90 days of resection was excluded from our analysis to focus specifically on the association of these factors on oncological outcomes after PD for PDA.

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS®) software version 20 (Chicago, Ill). For continuous variables t-test or Wilcoxon rank-sum test were performed depending on the distribution. Continuous variables are reported as median and range. Continuous variables were dichotomized at their median to compare them as two groups. Categorical variables were compared using Chi-Square test (χ^2) or Fisher's exact test and reported as number (n) and percentage (%). Survival data were computed using Kaplan-Meier method. Log-rank test was used to compare the categorical groups in univariate analysis. Predictors with a p value > 0.150 on univariate analysis were included in a multivariate Cox regression (Backward Stepwise -Wald) analysis. We subsequently performed a stepwise search that resulted in our final model. Statistical significance was achieved at $p < 0.05$.

RESULTS

Between January 2000 and December 2009, a total of 596 patients underwent PD for PDA. Demographic data are presented in Table 2. The ratio of male to female was 1:1 (294/302). The youngest patient in this cohort was 29 years old and the oldest was 92 years old. The median BMI was 26 (range 16–45). The majority of patients had biliary decompression prior to resection; 316 patients (53%) had endoscopic stenting, 22 patients (4%) had external biliary drainage and 8 patients (1%) had operative biliary bypass prior to resection. A minority of patients had neo-adjuvant therapy 27 (5%). The median follow up was 20 months (range 1–156 months). The overall median survival after PD for PDA was 24 months (Table 2).

Pathological analysis identified T3 disease in 97% of cases (579/596), and nodal positivity in 69% (411/596) of patients. Nearly all patients (97%) were found to have stage 2 disease. In 19% of the patients (112/596), the surgical margins were reported to be positive and all belong to R1. The median number of lymph nodes examined in the node-negative (N_0) group was 12 (range 2–31). The median number of lymph nodes examined in the node-positive (N_1) group was 14 (range 3–46). In the N_1 group the median number of nodes that were positive was 3 (range 1–21). Nodes were reported positive in 37% of patients (10/27) who underwent neoadjuvant therapy before resection.

The number of occurrences of low grade complications (Grade 1 and Grade 2) was 266 (45%) and high grade complications (Grade 3 and Grade 4) were 129 (22%). Operative mortality (Grade 5) within 90 days of surgery was 3.7% (22/596) (Table 2). The

gastrointestinal system was most commonly involved in the post-operative morbidity (19%) followed by skin (17%). The anastomotic fistula/leak or intra-abdominal abscess rate was 14%, followed closely by wound infection (13.8%) and delayed gastric emptying (5%). Among the anastomotic leaks, pancreatic leak was the most common (n=22), followed by biliary (n=11) and intestinal leak (n=2). 58% of anastomotic fistula/leak / intra-abdominal abscesses (48/82) were high grade and needed an intervention (Grade 3). High grade complications occurred in 22% of patients (6/27) who had neoadjuvant therapy and in 21% of patients (14/66) who underwent additional vascular procedure during PD.

The median blood loss was higher in the high grade group when compared to the low grade group (700 ml vs 600 ml, $p=0.276$) respectively and 21% of the patients (127/596) had blood product transfusion. The median operative time was similar between patients with high grade complications and low grade complications (284 minutes vs 283 minutes, $p=0.586$). Also presence of postoperative complication of any grade was not found to affect survival ($p=0.191$). The median length of hospital stay for patients in the high grade group was almost twice as long as those in the low grade group (17 days vs. 9 days, $p=0.001$).

The patient-, operative-, pathologic-, and postoperative variables that were analyzed for their association with overall survival are presented in Table 3. On univariate analysis node positivity (Figure 1), EBL 600 mL (Figure 2), ASA score 3, T-stage 3 and were associated with decreased survival ($p < 0.05$). Among the 13 variables listed only eight variables namely LOS >10 days, margin positivity, additional vascular procedure along with PD, age > 50, ASA 3, EBL 600 mL, T stage 3, node positivity, had a p value of 0.150 on univariate analysis based on log-rank test for overall survival. These factors were then included in a final step-wise multivariate Cox regression analysis. On multivariate analysis; node positivity, EBL 600 ml, LOS > 10 days, margin positivity and additional vascular procedures during PD predicted shorter survival. Among the independent predictors, node positivity was the strongest predictor of survival {HR= 1.81, ($p = 0.001$)} (Table 3). However, overall survival was independent of high grade (Grade 3 or higher) postoperative complications ($p=0.948$) (Figure 3).

DISCUSSION

PDA is an aggressive malignancy, with a five year survival rate of approximately 6% [9]. Patients with resectable pancreatic cancer have the best chance for long term survival. Due to the paucity of symptoms until advanced disease has developed, only 10–20% undergo resection [20]. Overall survival after resection for pancreatic cancer is dependent upon several well described factors such as nodal status, margin status, histological grade, post-resection CA 19-9 levels, tumor size, adjuvant therapy and hospital volume [10, 21–27]. Data from recent studies have suggested that postoperative morbidity may be associated with the long-term survival outcome after procedures for colorectal cancer [14–16], head and neck cancer [17] and esophageal cancer [18]. But the impact of postoperative morbidity after PD for PDA on long-term oncological outcome is still unclear.

Many authors have postulated that severe complications might lead to an extended period of immunosuppression which may allow residual tumor cells to proliferate in the host [28, 29].

Furthermore, others have suggested that these complications may result in a lack of adjuvant systemic therapy, with decreased survival secondary to lack of this treatment [30]. In this study, we evaluated for an association between high grade post-operative complications and overall survival after PD for PDA.

In our cohort, the high grade complication rate was 22% (n= 129). The most common complication was related to anastomotic fistula/leak/abscess (14%) followed by wound infection (13.8%) and delayed gastric emptying (5%) (Table 4). These data are not dissimilar from other large volume centers. In a large study comprising 1175 cases from John Hopkins, delayed gastric emptying, wound infection and pancreatic fistula were also the most common postoperative events; but their cohort also included patients who underwent total pancreatectomy (7% of cases) [6]. Our 90 day mortality rate of 3.7% for PD for PDA is consistent with current reports of 3–5% from other high-volume centers [6, 8]. Our cohort of 596 patients who underwent curative resection for PDA from 2001–2009 demonstrated a median survival of 24 months, figures that compare favorably with those reported in the literature [30].

On univariate analysis for overall survival ASA score, estimated blood loss > 600 ml, T stage (T ≥ 3), and nodal status were found to be associated with outcome ($p < 0.05$). Eight variables had a $p < 0.150$ on univariate analysis by log-rank test. Factors with a p value < 0.150 on univariate analysis were subsequently included in a multivariate Cox regression analysis. On multivariate analysis the most significant negative predictors of survival were nodal status (HR=1.81, $p= 0.001$) (Figure 1) and EBL >600 ml (HR=1.48, $p=0.001$) (Figure 2). A number of studies have confirmed that nodal status is a strong predictor for survival in pancreas cancer [12, 26, 31]. A study from John Hopkins in 2000 showed that EBL > 750 ml to be a negative predictor for survival after pancreas resection for PDA [32]. Blood loss has a clear association with transfusion and the immunosuppressive effects of transfusion in colon cancer are well known that can explain decreased survival [33]. Efforts to reduce blood loss and identifying risk factors in patients who are expected to receive transfusion, would therefore benefit most from blood conservation techniques. In our analysis, length of stay was a significant predictor of survival. Although complications can prolong length of stay and be a surrogate for high-grade complications, it is often multifactorial.

In our study, high grade complications after PD were not found to be associated with overall survival. Similarly, Assifi et al. reported that tumor recurrence after PD for PDA was independent of development of postoperative pancreatic fistula [34]. On the other hand, Nagai et al reported that pancreatic fistula was a negative predictor for tumor recurrence [35]. It has been reported that an inverse relationship exists between postoperative morbidity and the initiation of adjuvant therapy. After curative resection for hilar cholangiocarcinoma, patients who had major complications had a 26-month reduction in disease-specific survival and was associated with delay in adjuvant chemotherapy [36]. Similarly postoperative morbidity negatively impacted long-term outcomes in patients undergoing liver resection for colorectal metastasis with a low clinical risk score [16]. One reason these data are different than in other diseases is that the overall survival is so much shorter that there isn't time for complications to alter survival. Despite increasing evidence of survival benefit after adjuvant therapy, the results are far from optimal.

Our study has several limitations. It is a single-institution study. True pancreatic leaks may have occurred in some patients relative to other international standardized leak definitions and that the 14% leak rate may be peculiar to MSKCC definition. A significant percentage of our patients after resection follow up with their local medical oncologist and complete details of adjuvant therapy are not available. Therefore, we did not include adjuvant therapy in our analysis. Also, different oncologists have their own judgement for diagnosing recurrence; some are based on imaging, some oncologists perform biopsy to confirm recurrence and others rely on serial imaging and progression of symptoms and signs. Therefore in this study to avoid ambiguity, we did not include recurrence data.

In conclusion, PD for PDA was associated with a considerable rate of high grade complications (22%) in this study. Factors predictive of overall survival were node positive disease, margin positivity, EBL > 600 ml, additional vascular resections during surgery, and LOS > 10 days. High-grade complications were not found to be associated with long-term survival outcome.

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Synopsis

Pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDA) has a postoperative morbidity of 40–50%. In this study, we analyzed the impact of high grade postoperative complications after PD for PDA on overall survival. In this study, the occurrence of high grade postoperative complications was not associated with overall survival.

Figure 1. Survival curve for patients who are node negative (n= 180, black curve) and node positive (n=391, dotted grey curve)

Figure 2.
Survival curve for patients who have estimated blood loss (EBL) < 600ml (n=252, black curve) and EBL ≥ 600ml (n=309, dotted grey curve)

Figure 3.
Survival curve for patients who had no high grade complications (n=481, black curve) and high grade complications (n=90) (dotted grey curve)

Table 1

Definition and Grading Schema for the Pancreatic Leak (Memorial Sloan Kettering Cancer Center's Surgical Secondary Events Program)

Complications	Grade
Anastomotic leak, pancreas	
Clinical signs/symptoms or radiologic confirmation of pancreatic anastomotic leak with amylase-rich drainage > 50 mL/d beyond postoperative day 5, without development of fistula	1 Oral medication or bedside care required 2 IV medical therapy with resolution or antibiotics or TPN required 3 IR, endoscopic, or operative intervention required 4 Chronic deficit or disability associated with the event 5 Death associated with sequelae of this event

Table 2

Patient Demographics	n (%)
Total patients	596
Age- median (range)	69 (29–92)
Gender (Male/Female)	294/302
BMI- median (Range)	26 (16–45)
ASA1/2/3/4	4/310/277/5
Neo-adjuvant therapy	27 (5%)
Endoscopic biliary stenting	316 (53%)
External drainage	22 (4%)
Operative bypass	8 (1%)
Pre-operative albumin (> 3.5 g/dl)	450 (76%)
No complications (grade 0)	295 (49%)
Low grade * (grade 1 and 2)	266 (45%)
High grade * (grade 3 and 4)	129 (22%)
Death (90 days, grade 5)	22 (3.7 %)
Fistula/leak/intra-abdominal abscess *	82 (14%)
Median overall survival (months)	24

*
All occurrences

Table 3Univariate analysis for OS (n=571)[#] Multivariate analysis for OS (n=571)[#]

Variable	n	Median Survival (Months)	p value	HR	95% CI	p value
Lymph Node						
Negative	180	37	0.001	1.81	(1.47–2.22)	0.001
Positive	391	20				
EBL (in ml)						
<600	252	30	0.001	1.48	(1.23–1.78)	0.001
600	309	20				
LOS (in days)						
10	379	25	0.112	1.22	(1.01–1.48)	0.035
>10	192	21				
Margins						
Negative	464	24	0.074	1.27	(1.01–1.59)	0.040
Positive	107	20				
Vascular resection						
No	505	24	0.108	1.33	(1.01–1.75)	0.042
Yes	66	19				
ASA Score						
1 & 2	303	25	0.027	-	-	0.098
3 & 4	268	21				
T-stage						
T 2	15	79	0.021	-	-	0.590
T 3	554	23				
Age (in years)						
50	37	31	0.099	-	-	0.219
>50	534	23				
High grade complication						
Absent	481	23	0.812	-	-	0.948
Present	90	26				
Gender						
Female	286	26	0.350	-	-	-
Male	285	21				
BMI						
30	459	23	0.729	-	-	-
> 30	112	27				
Albumin (in g/dl)						
3.5	430	25	0.260	-	-	-
<3.5	136	20				
Operative time (in minutes)						
<284	283	26	0.339	-	-	-
>284	288	22				

OS-overall survival;

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90 days; HR- hazard ratio; CI- confidence interval; EBL-estimated blood loss ; LOS- length of stay; ASA-American Society of Anesthesiologists; T- tumor; BMI-body
#excluded patients if survival time
mass index

Table 4

Organ system	Type of complication	Number of occurrences ^a	% ^b	Total
Gastrointestinal System	Delayed gastric emptying	30	5.0	116
	Anastomotic Leak, Pancreas	22	3.7	
	Anastomotic Leak, Biliary	11	1.8	
	Gastrointestinal bleeding	10	1.7	
	Diarrhea	8	1.3	
	Ileus, paralytic	4	0.7	
	Cholangitis	4	0.7	
	Ascites	4	0.7	
	Constipation	3	0.5	
	Biloma	3	0.5	
	Fistula, Pancreatic	3	0.5	
	Fistula, Intestinal	2	0.3	
	Anastomotic Leak, Intestinal	2	0.3	
	Visceral Arterial Ischemia	2	0.3	
	Gastrointestinal Anastomotic Stricture	2	0.3	
	Fistula, Biliary	1	0.2	
	Pancreas Exocrine Insufficiency	1	0.2	
	Bile Reflux Gastritis	1	0.2	
	Biliary Stricture	1	0.2	
	Bowel Perforation, necrosis	1	0.2	
	Clostridium Difficile Colitis	1	0.2	
Wound or Skin	Wound Infection	82	13.8	104
	Fascial Dehiscence or Evisceration	8	1.3	
	Wound Breakdown	4	0.7	
	Cellulitis	3	0.5	
	Seroma	3	0.5	
	Skin Breakdown, Decubitus Ulcer	3	0.5	
	Abscess drainage	1	0.2	
Infection	Intra-abdominal Infection or Abscess	41	6.9	61
	Urinary Tract Infection	7	1.2	
	Sepsis	5	0.8	
	Multiple Organ System Failure	4	0.7	
	Fever	2	0.3	
	Catheter-related Infection	2	0.3	
Cardiovascular System	Supraventricular Arrhythmia	16	2.7	36
	Myocardial Infarction	5	0.8	
	Ventricular Arrhythmia	5	0.8	
	Congestive Heart Failure, left ventricular dysfunction	3	0.5	
	Hypotension, Shock	3	0.5	
	Angina, Cardiac Ischemia	2	0.3	

Organ system	Type of complication	Number of occurrences ^a	% ^b	Total
Hematologic and Vascular System	Vasovagal Episode	1	0.2	36
	Dysrhythmia	1	0.2	
	Hemorrhage	11	1.8	
	Pulmonary Embolus	8	1.4	
	Deep Venous Thrombosis	7	1.2	
	Anemia	7	1.2	
	Vascular Thrombosis	2	0.3	
Pulmonary System	Hematemesis	1	0.2	22
	Pneumonitis	8	1.3	
	Prolonged Intubation	6	1.0	
	Pleural Effusion	3	0.5	
	Aspiration	3	0.5	
	Acute Respiratory Distress Syndrome	1	0.2	
	Empyema	1	0.2	
Genitourinary System	Urinary Tract Infection	7	1.2	14
	Urinary Retention	6	1.2	
	Urinary Calculi	1	0.2	
General	Non-infected Intra-abdominal / Intra-thoracic fluid collection	7	1.2	13
	Dehydration	3	0.5	
	Progression of disease, death	3	0.5	
Nervous System	Cerebrovascular Accident	4	0.7	7
	Neuropathy, Motor	2	0.3	
	Psychosis, Confusion or Depression	1	0.2	
Metabolic	Acidosis	2	0.3	6
	Fluid Imbalance	2	0.3	
	Malnutrition	2	0.3	
Pain	Pain Syndrome, Acute	2	0.3	2

^aMany patients had > 1 complication;

^b% patients with that complications