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Oncologic and Perioperative Outcomes Following Selective Application of Laparoscopic Pancreaticoduodenectomy for Periapillary Malignancies

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Abstract

Background—Data are sparse regarding patient selection criteria or evaluating oncologic outcomes following laparoscopic pancreaticoduodenectomy (LPD). Having prospectively limited LPD to patients with resectable disease defined by National Comprehensive Cancer Network (NCCN) criteria, we evaluated perioperative and long-term oncologic outcomes of LPD compared to a similar cohort of OPD.

Methods—Consecutive patients (11/2010 – 02/2014) undergoing PD for periapillary adenocarcinoma were reviewed. Patients were excluded from further analysis for benign pathology, conversion to OPD for portal vein resection, and contraindications for LPD not related to their malignancy. Outcomes of patients undergoing LPD were analyzed in an intention-to-treat manner against a cohort of patients undergoing OPD.

Results—These selection criteria resulted in offering LPD to 77% of all cancer patients. Compared to the OPD cohort, LPD was associated with significant reductions in wound infections (16 vs. 34%; $P = .038$), pancreatic fistula (17 vs. 36%; $P = .032$) and median hospital stay (9 vs. 12 days; $P = .025$). Overall survival (OS) was not statistically different between patients undergoing LPD vs. OPD for periapillary adenocarcinoma (Median OS 27.9 vs. 23.5 mo; $P = .955$) or pancreatic adenocarcinoma ($N = 28$ vs. 22 patients; Median OS 20.7 vs. 21.1 mo; $P = 0.703$).

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Conclusions—The selective application of LPD for periampullary malignancies results in a high degree of eligibility as well as significant reductions in length of stay, wound infections and pancreatic fistula. Overall survival after LPD is similar to OPD.

Keywords

Laparoscopic; minimally invasive; pancreaticoduodenectomy; periampullary malignancy; pancreatic cancer; pancreatic surgery; long-term outcomes; overall survival

Introduction

Since the first description of pancreaticoduodenectomy (PD) in 1935 by Whipple¹, numerous refinements in patient selection, operative technique, and perioperative care have resulted in iterative improvements in outcomes for this potentially morbid procedure. In particular, regionalization of pancreatic surgery has proven a major effector of improved operative mortality and long-term survival.² Regionalization of pancreatic surgery has also facilitated innovation in the technical aspects of PD. Among these innovations, the application of minimally invasive approaches to PD has rapidly developed since its first description in 1994.³ In the past decade, several series report minimally invasive PD is not only feasible but may result in superior short-term outcomes.⁴⁻¹⁴ In fact, reduced blood loss, need for transfusion, and shorter hospital stays appear to be consistent advantages associated with laparoscopic PD (LPD).¹⁵ Most recently, Kendrick *et al.* reported that LPD performed for malignancy may be associated with improved long-term survival.¹⁴

However, these studies have not effectively addressed selection criteria or biases when offering minimally invasive or LPD. In fact, given concerns regarding the adequacy of the approach for adenocarcinoma, influential analyses of LPD range from universal inclusion¹⁴ to complete exclusion of all patients with known malignancy.¹³ Thus, there is currently a lack of data regarding appropriate oncologic selection criteria for LPD. Such criteria should ideally be driven by an assessment of both short- and long-term outcomes in patients that are selectively offered LPD. Thus, we analyzed a consecutive series of patients in whom a consistent set of selection criteria (resectable disease as defined by NCCN criteria) for exclusion of the LPD approach was utilized, comparing perioperative and overall survival to a cohort of OPD patients.

Methods

A prospectively maintained, IRB approved clinical database at the University of Florida was used to identify all consecutive patients who underwent PD between November, 2010 and February, 2014. Outcomes from patients selected to undergo LPD were compared against a cohort of patients undergoing PD by surgeons exclusively performing OPD over the same time period. All patients were identically managed per rigorous protocols throughout the perioperative period, including analgesia, antibiotics, fluids management, initiation of oral intake, and drain placement and removal.

The timeframe facilitated a minimum postoperative follow-up of 12 months to ensure that early and late complications as well as oncologic outcomes were evaluable. As our intent

was to assess selection criteria with respect to oncologic outcomes, patients that underwent PD for benign conditions, including pancreatic neuroendocrine tumors, were excluded from analysis. The study thus included all patients with periampullary adenocarcinoma with at least 12 months of follow-up.

The primary criteria for proceeding directly to OPD was based upon National Comprehensive Cancer Network (NCCN) criteria¹⁶ for borderline resectable disease: evidence of distortion, narrowing or occlusion of the superior mesenteric vein (SMV) or portal vein (PV), or abutment of the superior mesenteric artery (SMA) not exceeding 180 degrees of the circumference. The contraindications for LPD that were not related to the presence of a borderline resectable malignancy included morbid obesity as defined by a BMI 40, particularly unusual anatomy (i.e the duodenum and pancreatic head resided in the true pelvis), and previous surgery with prior operative notes that documented extensive adhesive disease (frozen abdomen).

Surgical technique was performed as previously described.¹⁷ Briefly, the laparoscopic pancreatojejunostomy is performed as an end-to-end intussuscepting anastomosis using a running, absorbable suture. The surgeons providing the comparison group all utilize an end-to-side, duct-to-mucosa technique without stenting. During LPD, all named arteries, particularly the gastroduodenal artery are not controlled with staples. Rather, this vessel is ligated at the origin from the hepatic artery with a silk suture, distally divided and further controlled with a 2.0mm staple load (to securely prevent retrograde hemorrhage from the distal lumen), and then clipped between the ligature and the staple line. Our group also consistently mobilizes the falciform ligament and rotates it as a flap to cover the hepatic artery.

For statistical analyses, the primary outcome was overall survival (OS). Secondary outcomes included intraoperative blood loss, need for transfusion, and 90-day postoperative complication rates. Postoperative complications were evaluated according to the previously validated Clavien-Dindo Classification¹⁸, with a specific focus on pancreatic fistula as defined by the International Study Group on Pancreatic Fistula (ISGPF) criteria.¹⁹

All statistical analyses were performed using the SPSS version 22.0 statistical software package (IBM SPSS statistics for Windows; IBM Corp). Continuous variables were analyzed using the independent samples *t*-test. Differences between categorical variables were analyzed using χ^2 coefficients. Kaplan-Meier survival curves were evaluated using the log-rank (or Mantel-Cox) test to calculate *P* values between groups. Univariate analysis was performed using a Cox Proportional Hazards Model. All variables significant (*P* < 0.05) on univariate analysis were included in multivariate Cox regression. Significance was considered for *P* < 0.05.

Results

Between November, 2010 and February, 2014, our institution performed 236 PDs. During this time frame, a single surgeon experienced in LPD performed a total of 124 PDs (91 LPD, 33 OPD). Over this same time frame, surgeons exclusively performing OPD performed 112

PDs. Taken together, 138 consecutive patients underwent PD for periampullary malignancy, excluding neuroendocrine pathology, and had at least 12 months follow-up. Patients were subsequently excluded from further analysis (fig. 1) if preoperative staging was outside NCCN criteria defining resectable lesions¹⁶ or if intraoperative findings identified mesoportal venous involvement by neoplasm requiring vein resection. The OPD cohort consisted of 61 patients undergoing PD for malignancy by pancreatic surgeons exclusively performing OPD. Of these 61 patients, 11 (18%) ultimately (by preoperative imaging or intraoperative findings) had borderline resectable disease as defined by NCCN criteria¹⁶ for PC requiring PV resection and were excluded from further analysis. In the LPD surgeon cohort, the operative indication was a periampullary malignancy in 77 patients. After excluding borderline resectable patients (per NCCN definition, $n = 13$) and patients for reasons not related to the underlying neoplasm ($n = 7$), 57 (74%) were offered LPD and 7 (9%) required intraoperative conversion. Intraoperative conversions were most commonly due to the underestimation of disease burden on preoperative imaging requiring vein resection (5/7). As these patients would not have been offered LPD by preoperative intention and could not be appropriately compared to the OPD cohort, these five patients were excluded from further analysis. The two other causes of intraoperative conversion included a hepatic artery injury in the setting of extensive peripancreatic inflammation (1/7) and SMV laceration that could not be controlled laparoscopically (1/7). These two cases were included in the intent-to-treat analysis.

Preoperative clinical parameters and pathologic diagnosis are displayed for each group in Table 1. Statistical analysis confirmed that the two cohorts were similar with respect to age, comorbidities, sex and BMI. Pathologic diagnoses were also statistically equivalent between LPD and OPD groups.

LPD was associated with a significant reduction in blood loss (Table 2). However, transfusions rates were equivalent between groups. Given the exclusion criteria, vascular resection was not performed laparoscopically or in the OPD cohort. The LPD cohort was similar with respect to neoadjuvant chemotherapy, tumor grade and lymphatic stage. The average tumor size (cm in greatest dimension) in the LPD cohort was slightly smaller than that observed in the OPD cohort (2.5 cm vs 3.1 cm). LPD was associated with a 91% R0 resection rate compared to 74% in the OPD cohort ($P = .030$). Both cohorts demonstrated adequate and similar lymph node yields.

Operative complications for each cohort are displayed in Table 3. Complications were analyzed using the Clavien-Dindo classification¹⁸ with a specific focus on pancreatic fistula, graded according to the International Study Group on Pancreatic Fistula (ISGPF) criteria.¹⁹ LPD was associated with significant reductions in pancreatic fistula (17 vs. 36%; $P = .032$) and hospital stay (9 vs. 11.9 days; $P = .025$). LPD was also associated with a reduction in postoperative wound infections (16 vs. 34%; $P = .038$). Despite these improvements similar rates of major morbidity were observed, defined as Clavien III/IV complications. One patient in the LPD cohort died within 30 days of the operation due to post-pancreatectomy hemorrhage.

Overall survival was not significantly different between LPD and OPD for all patients with periampullary adenocarcinoma (Median OS 27.9 vs. 23.5 mo; $P = .955$) as well as the subset with PC (Median OS 20.7 vs. 21.1 mo; $P = .703$) (Fig 2). Univariate analysis confirmed the predictive value of known prognostic factors on overall survival (Table 4). Specifically, LN stage and poor tumor differentiation conferred reduced overall survival. Additionally, the receipt of a blood transfusion intraoperatively significantly correlated with reduced long-term survival. Exclusive analysis of PC revealed similar associations with survival.

All parameters demonstrating statistically significant associations with survival on univariate analysis ($P < .05$) were incorporated into respective multivariate analyses (Table 4) with operative approach. Poor tumor differentiation and positive lymph node ratio significantly associated with survival on multivariate analysis in patients with periampullary adenocarcinoma. Again, operative approach demonstrated no significant correlation with overall survival.

Discussion

As an initial step in defining selection criteria for the application of minimally invasive techniques to periampullary adenocarcinoma, we present short- and long-term outcomes of patients following the consistent application of LPD for resectable lesions as defined by NCCN criteria. This approach led to a high percentage of cancer patients being candidates for LPD, a high R0 resection rate, and a low conversion rate. Overall survival was equivalent between LPD and OPD.

All significant parameters in this analysis predictive of outcome have been previously established to convey high prognostic value in other series.^{20, 21} Our analysis confirms the prognostic value of tumor stage and grade, and this finding would suggest that this series contains a representative population. Applying multivariate analysis in this context again confirms no apparent association between operative approach and long-term survival in the treatment of periampullary adenocarcinoma.

To date, the majority of series evaluating LPD have identified reductions in blood loss, wound infections and hospital stay when compared to OPD.²² Our findings are in line with these previous reports. The relationship between blood loss, transfusion and overall survival has been previously established in several large OPD series.^{20, 23} Kendrick *et al.* recently reported improved disease-free survival in a cohort of 108 patients with pancreatic adenocarcinoma undergoing LPD, including patients that underwent vein resection/reconstruction, compared to 214 patients undergoing OPD.¹⁴ Overall survival was not significantly different between groups. While our results reinforce a strong association between intraoperative transfusion and overall survival, we demonstrate similarly low rates of transfusion (8-12%) between LPD and OPD cohorts when borderline resectable disease is excluded. Thus, the enticing notion that LPD reduces the need for blood transfusion and may confer a benefit in oncologic outcome is not reinforced by our data, but this is in the context of exclusion of borderline resectable lesions, a potentially inadequate sample size, and cohorts that slightly differed in tumor size.

Regarding the selection criteria for offering LPD, it is important to note that long-term outcomes had not been evaluated in LPD for malignancy at the time of study initiation. We therefore exercised caution with our approach toward perampullary adenocarcinomas, using NCCN criteria for borderline resectable lesions to avoid positive margins or engage in the technical demands and possible adverse outcomes that could be associated with venous resection and reconstruction. Borderline resectable disease was the factor that prompted ineligibility for LPD in the majority of cases and was the primary indication for conversion to OPD. However, our results only provide a baseline upon which the forwarded selection criteria may subsequently be expanded or contracted. For example, others have demonstrated the feasibility of major vascular resection in LPD.²⁴ With the inclusion of these patients, one could anticipate LPD being offered to the vast majority of patients with perampullary malignancy, but such an expansion of inclusion criteria will need to be balanced with the ability to obtain a R0 resection and minimize intraoperative blood loss and associated transfusions.

In summary, we conclude that the selective application of LPD led to high percentage of pancreatic and perampullary cancer patients being candidates for LPD, a high R0 resection rate, a low conversion rate, improved short-term and equivalent long-term oncologic outcomes.

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Fig 1. Patient Selection and Analysis

A schematic detailing patient selection and analysis is displayed. As eligibility for LPD generally centered around the absence of borderline resectable disease, open cohorts were dichotomized based on these criteria. Borderline resectable disease was anatomically defined by current NCCN criteria that include: involvement of the SMV or PV with distortion, narrowing or occlusion that can be reconstructed or abutment of the SMA not exceeding 180 degrees of the circumference.¹⁶ LPD, laparoscopic pancreaticoduodenectomy; BMI, body mass index; SMV, superior mesenteric vein; PV, portal vein; SMA, superior mesenteric artery.

Fig 2. Kaplan-Meier Survival Curves

Overall survival is displayed for patients with periapillary adenocarcinoma (*left*) and pancreatic cancer (PC) only (*right*) in LPD and OPD cohorts.

Table 1**Patient Demographics and Diagnoses**

	LPD (n = 52)	OPD (n = 50)	P Value
Age, mean (SE)	65.3 (1.7)	68.6 (1.4)	.127
Charlson Comorbidity Index, mean (SE)	5.8 (0.2)	6.0 (0.2)	.466
Male, %	34 (65)	28 (56)	.332
BMI, mean (SE)	26.3 (0.8)	25.5 (0.7)	.455
Neoadjuvant therapy, %	3 (6)	3 (6)	1.00
Pathologic Diagnosis			
Pancreatic Adenocarcinoma (PC), %	28 (54)	22 (44)	.320
Cholangiocarcinoma (CC), %	10 (19)	8 (16)	.669
Ampullary Adenocarcinoma (AC), %	13 (25)	17 (34)	.319
Duodenal Adenocarcinoma (DC), %	1 (2)	3 (6)	.358

P values were calculated using the unpaired *t* test for continuous variables and χ^2 coefficients for categorical variables. Abbreviations: SE, standard error.

Table 2

Operative and Oncologic Factors

	LPD (n = 52)	OPD (n = 50)	P Value
Operative Time (min), mean (SE)	361 (7)	360 (9) ^{##}	.941
EBL (mL), mean (SE)	260 (36)	518 (54)	<.001*
Transfusion, %	4 (7.7)	4 (8.2)	1.00
Portal Vein Resection, %	0	0	1.00
Nodal Metastasis, %	34 (65.4)	40 (80.0)	.098
Total Lymph Nodes, mean (SE)	23.0 (1.2)	20.8 (1.2)	.178
Positive Lymph Nodes, mean (SE)	3.1 (0.5)	3.1 (0.4)	.994
Tumor Size (cm), mean (SE)	2.5 (0.1)	3.1 (0.2)	.046*
R1 Resection, %	5 (9.6)	13 (26.0)	.030*
Poor Differentiation, %	24 (47.1) [#]	24 (49.0) [#]	.848

R0 resection is defined as a margin-negative resection.

[#] One adenosquamous tumor was excluded from analysis of tumor differentiation in each indicated cohort.

^{##} Operative times were available for 42 of 50 OPD patients. *P* values represent significant levels calculated using the unpaired *t* test for continuous variables and χ^2 coefficients for categorical variables. Significance was considered for *P* < 0.05.

Table 3

Postoperative Complications

	LPD (n = 52)	OPD (n = 50)	P Value
Length of Stay (d), mean (SE)	9.0 (0.7)	11.9 (1.1)	.025*
Wound Infection (%)	8 (16)	17 (34)	.038*
Pancreatic Leak, %	9 (17)	18 (36)	.032*
Grade B/C Leak, %	6 (12)	13 (26)	.061
Postpancreatectomy Hemorrhage (%)	5 (10)	3 (6)	.716
Major Morbidity (Clavien III/IV)	13 (25)	16 (32)	.433
30-Day Mortality, %	1 (2)	0	1.00

Pancreatic fistulas are graded according to the International Study Group on Pancreatic Fistula (ISGPF) criteria.¹⁹ Morbidity is defined by Clavien-Dindo classification, as previously described.¹⁸ *P* values were calculated using χ^2 coefficients for categorical variables and the unpaired *t* test for continuous variables. Abbreviations: d, days.

Table 4

Overall Survival

Univariate Analysis						
	Periampullary Adenocarcinoma (n = 102)			Pancreatic Adenocarcinoma (n = 50)		
	HR	95% CI	P Value	HR	95% CI	P Value
Age (y)	1.02	0.99 – 1.05	.131	1.02	0.98 – 1.06	.428
BMI	0.99	0.93 – 1.04	.580	1.00	0.94 – 1.08	.919
Charlson Comorbidity Index	1.20	0.98 – 1.46	.080	0.97	0.77 – 1.23	.802
Diagnosis (PC vs. non-PC)	1.25	0.73 – 2.12	.415	N/A	N/A	N/A
Neoadjuvant Chemo/XRT	1.04	0.37 – 2.87	.947	1.20	0.42 – 3.48	.736
Poor Tumor Differentiation	2.59	1.48 – 4.50	.001	2.81	1.30 – 6.07	.008
Nodal Metastasis	2.52	1.23 – 5.15	.012	2.56	0.77 – 8.49	.124
Positive Lymph Node Ratio	6.12	1.83 – 20.5	.003	4.68	0.76 – 29.0	.097
Tumor Size (cm)	0.96	0.80 – 1.15	.642	0.88	0.64 – 1.22	.455
R1 Resection	1.51	0.81 – 2.81	.198	1.20	0.53 – 2.72	.663
Estimated Blood Loss (L)	0.92	0.45 – 1.88	.816	1.00	0.34 – 2.95	.994
Intraoperative Transfusion	2.44	1.10 – 5.44	.028	2.14	0.74 – 6.23	.162
LPD (vs. OPD)	0.95	0.56 – 1.62	.858	1.16	0.55 – 2.46	.703
Multivariate Analysis						
Poor Tumor Differentiation	3.06	1.70 – 5.51	<.001	2.82	1.31 – 6.09	.008
Intraoperative Transfusion	1.80	0.76 – 4.27	.181	N/A	N/A	N/A
Positive Lymph Node Ratio	9.72	2.25 – 42.1	.002	N/A	N/A	N/A
LPD (vs. OPD)	0.89	0.51 – 1.54	.668	1.07	0.50 – 2.29	.872

Survival analysis of 100 patients undergoing PD for periampullary adenocarcinoma and PC only was performed using a univariate Cox proportional hazards model. Positive lymph node ratio is defined as the number of lymph nodes positive for malignancy divided by the total number of lymph nodes examined. A multivariate Cox proportional hazards model was then constructed by incorporating all significant variables employed in univariate analysis.

* Significance was considered for $P < 0.05$.