ORIGINAL ARTICLE

Comparative Effectiveness of Minimally Invasive and Open Distal Pancreatectomy for Ductal Adenocarcinoma

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Importance: Multicenter studies indicate that outcomes of open (ODP) and minimally invasive distal pancreatectomy (MIDP) are equivalent for benign lesions. However, data for pancreatic carcinoma are limited.

Objective: To compare outcomes of ODP and MIDP for early-stage pancreatic ductal carcinoma to determine relative safety and oncologic efficacy.

Design: Retrospective analysis of 62 consecutive patients undergoing ODP or MIDP for pancreatic ductal carcinoma by intention to treat with propensity scoring to correct for selection bias.

Setting: A high-volume university center for pancreatic surgery.

Participants: Sixty-two patients at a single institution.

Interventions: Patients underwent ODP or MIDP.

Main Outcome Measures: Perioperative mortality, morbidity, readmission, postoperative complications, disease progression, and overall survival.

Results: Thirty-four patients underwent ODP, and 28 underwent MIDP with 5 conversions to ODP. No significant differences in age, body mass index, performance status, tumor size, or radiographic stage were identified. High rates of margin-negative resection (ODP, 88%; MIDP, 86%) and median lymph node clearance (ODP, 12; MIDP, 11) were achieved in both groups with equal rates and severity of postoperative complications (ODP, 50%; MIDP, 39%) and pancreatic fistula (ODP, 29%; MIDP, 21%). Despite conversions, intended MIDP was associated with reduced blood loss ($P = .006$) and length of stay ($P = .04$). Conversion was associated with a poor histologic grade and positive nodes. Median overall survival for the entire cohort was 19 (95% CI, 14-47) months. Minimally invasive distal pancreatectomy was performed increasingly in later study years and for patients with a higher Charlson–Age Comorbidity Index. Overall survival after ODP or intended MIDP was equivalent after adjusting for comorbidity and year of surgery (relative hazard, 1.11 [95% CI, 0.47-2.62]).

Conclusions and Relevance: We detected no evidence that MIDP was inferior to ODP based on postoperative outcomes or overall survival. This conclusion was verified by propensity score analysis with adjustment for factors affecting selection of operative technique.

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Minimally invasive surgery reduces the short-term perioperative morbidity of distal pancreatectomy for benign tumors and has a safety profile equivalent to that of open procedures.[1-4] Conversely, no consensus exists regarding the oncologic efficacy of minimally invasive surgery for pancreatic ductal carcinoma (PDC), although 71.4% of Americans with stage I PDC currently forgo potentially curative surgical treatment in the modern era.[5]

Two methodological problems complicate prospective studies of the effect of a surgical procedure on survival of early-stage PDC arising in the distal pancreas. First, only 20.8% of PDC arises in the distal pancreas. Second, annual distal pancreatectomy case volume in the United States averages 1 per hospital in the 1998-2003 Nationwide Inpatient Sample.[6] Consequently, published comparative effectiveness research is retrospective and confined to single-institution data.[1,7,8] A single study of laparoscopic distal pancreatectomy (LDP) for PDC evaluated outcomes in 23 patients at 9 centers and demonstrated median survival (16 months) identical to that for open procedures by means of a 3:1 matched comparison.[1]

We hypothesize that open (ODP) and minimally invasive distal pancreatectomy (MIDP) are equivalent procedures

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for pancreatic cancer among expert surgeons. We compared perioperative outcomes and survival in 62 consecutive patients undergoing ODP or MIDP for potentially resectable PDC at a single institution from 2002 through 2010. We performed intention-to-treat analysis with propensity score adjustment for selection bias within the study population. These data provide the basis for a nationwide study comparing the relative effectiveness of MIDP and ODP for PDC of the pancreatic body and tail.

METHODS

STUDY POPULATION AND DESIGN

This retrospective study was approved by the University of Pittsburgh institutional review board. Sixty-two consecutive patients underwent evaluation after surgical resection for distal PDC from March 1, 2002, through November 30, 2010. The study interval coincided with the first MIDP at University of Pittsburgh Medical Center to collect contemporaneous outcomes of ODP. The first MIDP for PDC was performed after an institutional experience of 30 cases for benign disease. The choice of surgical technique was made by 6 experienced pancreatic surgeons (including S.J.H., K.K.W.L., H.J.Z., and A.J.M.) at a high-volume center. The MIDP cohort (n=28) included laparoscopic (n=20) and robot-assisted (n=8) (da Vinci System; Intuitive Surgical) procedures.

ELIGIBILITY, DATA COLLECTION, AND DEFINITIONS OF OUTCOME

We analyzed patient demographics, imaging, operative summaries, anesthesia logs, pathology reports, discharge summaries, and medical oncology records. Measures of functional status included Karnofsky performance status,[9] American Society of Anesthesiologists physical status,[10] and Charlson–Age Comorbidity Index (CCI).[9,11-13] Exclusion criteria consisted of suspected borderline resectable or locally advanced disease according to National Comprehensive Cancer Network guidelines,[11] prior chemotherapy and/or radiotherapy for PDC, and incomplete follow-up.

Perioperative mortality was defined as death during the index hospitalization or within 30 days. Morbidity and readmission were monitored for 90 days. Readmission was defined as any additional hospitalization, excluding admission to a subacute care or rehabilitation facility. Pancreatic fistulae were graded by the International Study Group on Pancreatic Fistula.[14-16] Postoperative complications were graded using the Clavien-Dindo classification.[17] Overall survival was defined as the duration from the date of surgery to death from any cause. Time to progression was calculated from the date of surgery to the date of tumor recurrence or death from any cause, and the location of the first recurrence was recorded.

PATHOLOGICAL EVALUATION

Pathological assessment included traditional TNM metrics and detailed secondary assessments (performed by A.K.) of margin status at the transected surface of the pancreas and the radial margins. The proximity of microscopic tumor to the final surgical margin was measured in millimeters to quantify the effect of surgical technique on the completeness of margin clearance.

PROPENSITY SCORING

A propensity score is a predicted probability derived from a logistic regression model that a patient was selected for ODP or MIDP. The propensity score equilibrates comparison arms in an observational study as if the treatments had been randomly assigned. The propensity score adjusted outcomes for surgeon bias in the selection of surgical technique and for the effect of time on the duration of follow-up caused by the adoption of MIDP toward the end of the study period. Numerous preoperative factors were tested, including age, sex, body mass index, imputed computed tomography (CT) stage, tumor size, CCI, American Society of Anesthesiologists physical status, Karnofsky performance status, year of procedure, and identity of the surgeon. Of these covariates, only CCI and year of surgery were significantly associated with the propensity to perform MIDP.

STATISTICAL ANALYSIS

Outcomes were analyzed on an intent-to-treat basis. We tested differences in continuous variables using the Wilcoxon test (2 groups) or Kruskal-Wallis test (3 groups); we used the Fisher exact test for categorical variables. Raw *P* values were reported for each test, and adjustments for multiple comparisons were not performed. We estimated overall survival using the Kaplan-Meier method with Greenwood confidence intervals. Overall survival for ODP and MIDP was compared with a Cox proportional hazards regression model that included propensity score as a covariate. Thus, the comparison of the 2 cohorts is adjusted for differences in preoperative selection factors. In addition, we adjusted survival estimates based on surgical pathological findings as needed.

RESULTS

PATIENT-RELATED FACTORS AFFECTING SURGICAL TECHNIQUE

Sixty-two patients underwent distal pancreatectomy, including 34 ODP (55%) and 28 MIDP (45%). Median observation time for the entire cohort was 25 (range, 5-101) months for patients alive at the end of the study. Eight patients were alive in the ODP cohort at a median follow-up of 31 months, whereas 17 patients were alive after MIDP at a median follow-up of 21 months, reflecting the recent adoption of MIDP.

Patients undergoing MIDP and ODP for PDC were functionally independent with equivalent demographic characteristics (**Table 1**). Both cohorts were well matched for age, sex, race, body mass index, American Society of Anesthesiologists physical status, and prior abdominal surgery. Karnofsky performance status and CCI were also equivalent (median CCI, 3 for the MIDP cohort vs 1 for the ODP cohort).

IMAGING FACTORS AFFECTING PATIENT SELECTION

All patients underwent preoperative CT. Forty-six (74%) also underwent endoscopic ultrasonography (EUS) (**Table 2**). Imaging characteristics were used to assign a preoperative stage using American Joint Committee on Cancer (AJCC) criteria. Imputed AJCC stage was formulated on the basis of (1) tumor diameter (T1 vs T2),

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Table 1. Demographic Characteristics of the Study Population

Patient Factor	Procedure		*P* Value
	ODP (n = 34)	MIDP (n = 28)	
Age, mean (SEM), y	66 (2.0)	67 (2.2)	.82
Female sex, No. (%)	21 (62)	19 (68)	.62
White race, No. (%)	30 (88)	22 (79)	.41
BMI, mean (SEM)	26.5 (0.7)	26.7 (1.3)	.29
Karnofsky performance status, median (IQR)	90 (80-90)	90 (80-90)	.81
CCI, median (IQR)	1 (0-4)	3 (0-5)	.38
ASA physical status, median (IQR)	3 (2-3)	3 (3-3)	.11
Prior abdominal surgery, No. (%)	19 (56)	18 (64)	.59

Abbreviation: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCI, Charlson–Age Comorbidity Index; IQR, interquartile range; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy.

(2) evidence of adjacent vascular or solid organ involvement (T3/T4 vs none), and (3) appearance of abnormal lymph nodes (N0 vs N1). Tumor measurements by means of CT and EUS were equivalent. No patients had radiographic evidence of T4 lesions. The CT and EUS criteria provided no evidence of a more advanced radiographic stage in the ODP group; T3 lesions and/or abnormal lymph nodes ($P = .45$) were suspected among 17 (50%) ODP patients and 11 (39%) MIDP patients. The cohorts were similarly well matched by EUS criteria: 65% of the ODP patients and 61% of the MIDP patients had EUS stage I tumors, whereas 35% of the ODP patients and 39% of the MIDP patients had stage II tumors. The percentage of patients with lymph nodes assessed as abnormal was similar using preoperative CT (6 of 31 ODP patients [19%] vs 4 of 23 MIDP patients [17%]) and EUS (5 of 23 ODP patients [22%] vs 6 of 23 MIDP patients [26%]).

PERIOPERATIVE OUTCOMES

All 5 MIDP procedures converted to ODP were attempted laparoscopically (5 of 20 patients) (**Table 3**). Intraoperative factors identified as causes for conversion included failure to progress owing to dense adhesions (n = 1), technical difficulty transecting the proximal splenic artery (n = 1), bleeding owing to inadvertent splenic artery injury (n = 1), and adjacent visceral invasion requiring en bloc resection (n = 2).

Outcomes after MIDP were equivalent or superior to those after ODP on the basis of intention-to-treat analysis. Mean (SEM) operative time (294 [24] for the ODP cohort vs 317 [23] minutes for the MIDP group), transfusion risk (6 of 28 MIDP patients [21%] vs 14 of 34 ODP patients [41%]; $P = .31$), and rates of postoperative readmission to the intensive care unit (3 of 28 intended MIDP and 0 of 34 intended ODP) during the index hospitalization were equivalent. Mean (SEM) intraoperative blood loss (290 [60] vs 570 [80] mL; $P = .006$) and median (interquartile range [IQR]) index hospitalization length of stay (6 [2.8] vs 8 [3.0] days; $P = .03$) were superior after MIDP compared with ODP.

Table 2. Imaging Characteristics and AJCC Stage Assigned on the Basis of Preoperative CT and EUS

Imaging Characteristic	Procedure		*P* Value
	ODP (n = 34)	MIDP (n = 28)	
CT measurement of tumor, median (IQR), cm	3.0 (2.1-3.7)	3.0 (2.2-3.6)	.99
CT-determined stage, No. (%)[a]			
IA	3 (10)	3 (13)	.83
IB	12 (39)	11 (48)	
IIA	10 (32)	5 (22)	
IIB	6 (19)	4 (17)	
EUS measurement of tumor, median (IQR), cm	2.6 (2.2-2.8)	2.6 (2.2-3.0)	.78
EUS-determined stage, No. (%)[b]			
IA	4 (17)	6 (26)	.87
IB	11 (48)	8 (35)	
IIA	3 (13)	3 (13)	
IIB	5 (22)	6 (26)	

Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; EUS, endoscopic ultrasonography; IQR, interquartile range; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy.

[a] All 62 study patients underwent CT, of which 54 (ODP, 31; MIDP, 23) could be assigned an imputed AJCC stage based on radiographic criteria.

[b] Forty-eight patients underwent EUS, of which 46 could be assigned an imputed AJCC stage by ultrasonographic criteria.

Table 3. Perioperative Outcomes After ODP and MIDP for PDC

Outcome Variable	Procedure		*P* Value
	ODP (n = 34)	MIDP (n = 28)	
Length of stay, median (IQR), d	8 (3)	6 (2.75)[a]	.03
Estimated blood loss, median (SEM), mL	570 (80)	290 (60)	.006
Perioperative transfusion, No. (%)	14 (41)	6 (21)	.78
Severity of perioperative complications grade, No. (%)[a]			
I	6 (55)	5 (83)	.73
II	4 (36)	1 (17)	
III	1 (9)	0	
Postoperative complications, No. (%)	17 (50)	11 (39)	.45
Pancreatic fistula, No. (%)	10 (29)	6 (21)	.57
ISGPF Grade A	7 (70)	5 (83)	
ISGPF Grade B	3 (30)	1 (17)	
Readmissions within 90 d, No. (%)	12 (35)	10 (36)	>.99
Total length of stay including any re-admission, median (IQR), d	9 (8)	7 (5)	.04

Abbreviations: IQR, interquartile range; ISGPF, International Study Group of Pancreatic Fistula; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy; PDC, pancreatic ductal carcinoma.

[a] Graded using the Clavien-Dindo classification (defined as all medical and potential postsurgical events).

The frequency and severity of postoperative complications were equivalent for both procedures using the Clavien-Dindo classification (11 of 28 MIDP patients [39%] vs 17 of 34 ODP patients [50%]) (Table 3). Pancreatic fistula rates were similar (6 of 28 MIDP patients [21%] vs 10 of 34 ODP patients [29%]), with only 1 clinically significant fistula in the MIDP group and 3 in the ODP group. No reoperations or deaths occurred. Ninety-day

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Table 4. Pathological Outcomes After MIDP and ODP for PDC

Variable	Procedure		*P* Value
	ODP (n = 34)	MIDP (n = 28)	
R0 resection, No. (%)	30 (88)	24 (86)	>.99
Margin distance, mm[a]			
>2	21 (70)	18 (75)	
≤2	7 (23)	2 (8)	.38
Positive margins, No. (%)	4 (12)	4 (14)	
Total lymph node clearance, median (IQR)	12 (6-19)	11 (8-20)	.75
Size, median (IQR), cm	4.5 (2.8-5.4)	3.7 (2.8-4.5)	.17
Differentiation grade			
Well	1 (3)	3 (11)	
Moderate	20 (59)	11 (39)	.24
Poor	13 (38)	14 (50)	
N1, No. (%)	13 (38)	16 (57)	.07
Lymph node ratio, mean (SEM)	0.08 (0.02)	0.14 (0.04)	.14
AJCC stage			
IA	2 (6)	3 (11)	
IB	5 (15)	1 (4)	
IIA	14 (41)	8 (30)	.25
IIB	12 (35)	16 (59)	
III	1 (3)	0	

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy; PDC, pancreatic ductal carcinoma.

[a] Margin distance could not be measured in 6 surgical pathological specimens (2 patients undergoing ODP and 4 undergoing MIDP).

readmission rates were similar (36% after MIDP; 35% after ODP), and surgical technique had no effect on the causes or the severity of readmission events (data not shown). Total hospital stay including readmissions to 90 days was significantly shorter after MIDP (median [IQR], 7 [5] days) than after ODP (9 [8]; *P* = .04).

PATHOLOGICAL OUTCOMES

Pathological outcomes in the 2 cohorts were equivalent (**Table 4**). Lymph node clearance was identical (median number, 12 for ODP vs 11 for MIDP). No differences in tumor size or histologic grade were observed. The distribution of AJCC stages was similar, with a trend toward a higher likelihood of positive nodes in the MIDP group (N1, 57% vs 38%, *P* = .07).

The margin-negative resection rate (R0) was 88% after ODP and 86% after MIDP (*P* > .99) (Table 4). Four positive-margin outcomes were found in each group. Two of 4 MIDP patients with positive margins underwent conversion to open procedures before completion. The analysis of margin distance in each cohort demonstrated no adverse effect of MIDP on soft-tissue clearance (Fisher exact test, *P* = .38).

ADVERSE OUTCOMES ASSOCIATED WITH CONVERSION TO ODP

Five patients (18%) in the intended MIDP group underwent conversion to ODP (**Table 5**). All 5 conversions occurred during the first 12 attempted minimally invasive resections for PDC (42%); no conversions occurred in the rest of the series (*P* = .007). Cumulative surgical experience was the only preoperative factor associated with conversion; age, sex, CCI, Karnofsky performance status, body mass index, and tumor diameter had no effect on completion of MIDP.

Table 5. Pathological Factors Associated With Conversion From MIDP to ODP

Pathological Factor	Procedure			*P* Value
	ODP (n = 34)	MIDP (n = 23)	Conversion to ODP (n = 5)	
Median tumor size, cm	4.5	3.5	4.6	.15
Poorly differentiated, No. (%)	13 (38)	9 (39)	5 (100)	.04
Positive margin, No. (%)	4 (12)	2 (9)	2 (40)	.19
Lymph node positive, No. (%)	13 (38)	13 (57)	5 (100)	.03
Lymph node ratio, mean	0.22	0.13	0.22	.03

Abbreviations: MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy.

Although case order affected technical outcomes, advanced surgical pathological findings were also associated with conversion. All patients undergoing conversion to ODP (100%) had poorly differentiated tumors compared with 38% among ODP patients and 39% among MIDP patients in whom the procedure was completed (*P* = .04). The proportion of patients with positive lymph nodes (100% in patients undergoing converted procedures vs 57% in completed MIDP and 38% in completed ODP) and the mean lymph node ratio were also significantly greater (*P* = .03) among patients with conversion to open procedures. These data suggest that intraoperative recognition of advanced pathological findings, and particularly nodal status, contributed to the decision to convert.

Patients requiring conversion from MIDP to ODP experienced longer median hospitalization compared with patients undergoing completed MIDP (median, 6 to 8 [IQR, 3] days; *P* = .002) but no change in intraoperative blood loss, transfusion risk, or admission to the intensive care unit. Four of 5 patients undergoing conversion experienced at least 1 adverse event, including grade 3 wound infection in the presence of a pancreatic fistula (n = 1), grade 2 intra-abdominal hemorrhage (n = 1), and grade 1 or 2 medical events (n = 3), but the resulting complication rate did not reach statistical significance (*P* = .10) compared with successful MIDP (7 of 23 [30%]), converted MIDP (4 of 5 [80%]), or planned ODP (17 of 34 [50%]).

PROPENSITY SCORE ANALYSIS

The probability of undergoing ODP declined from 8 of 8 total procedures in 2002 to 2003 to 1 of 9 in 2009 (**Figure 1**A). We identified a higher CCI and the year of surgery as the only factors affecting the propensity to perform MIDP. No demographic or imaging findings influenced the selection of surgical technique.

As shown in Figure 1B, the odds of receiving MIDP for PDC increased for patients with a CCI of 2 in all years relative to 2002. Similarly (Figure 1C), the odds

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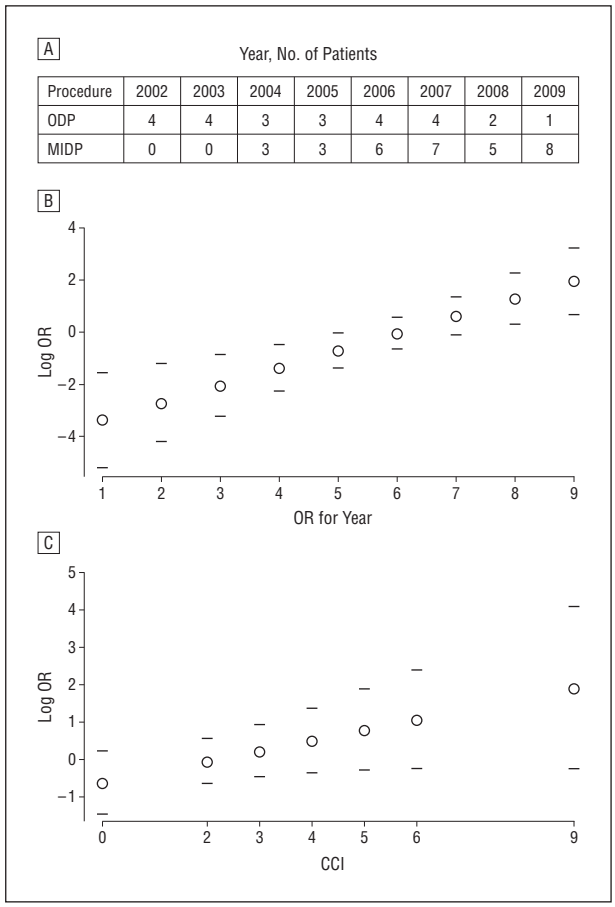


Figure 1. Propensity analysis based on a logistic regression model logarithm of the odds ratio (log OR) for attempting minimally invasive distal pancreatectomy (MIDP) at the University of Pittsburgh Medical Center (UPMC). A, Accrual to open distal pancreatectomy (ODP) and MIDP by study year. B, Propensity to perform MIDP relative to year 1 (2002) adjusted to a Charlson–Age Comorbidity Index (CCI) of 2. The OR for MIDP increased progressively from 2002 (year 1) to 2010 (year 9). C, Log OR for attempting MIDP at UPMC as a function of the CCI adjusted to year 2007. The OR for attempting MIDP increased across the range of CCIs from 0 to 9, indicating that patients with more medical comorbidities were more likely to undergo MIDP with time relative to ODP. Whiskers represent 95% confidence intervals.

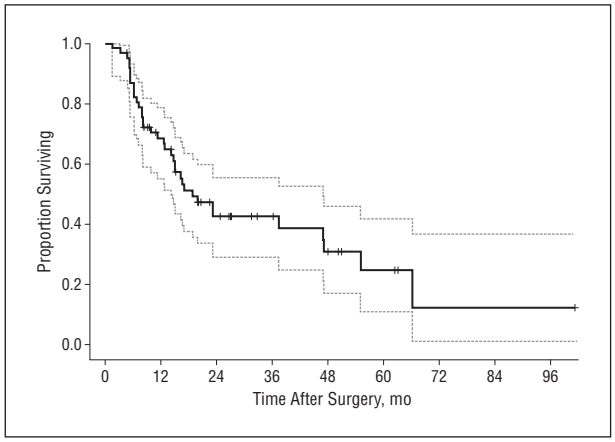


Figure 2. Median overall survival for all patients undergoing distal pancreatectomy and adjuvant therapy for pancreatic ductal carcinoma. Dotted lines indicate 95% confidence intervals.

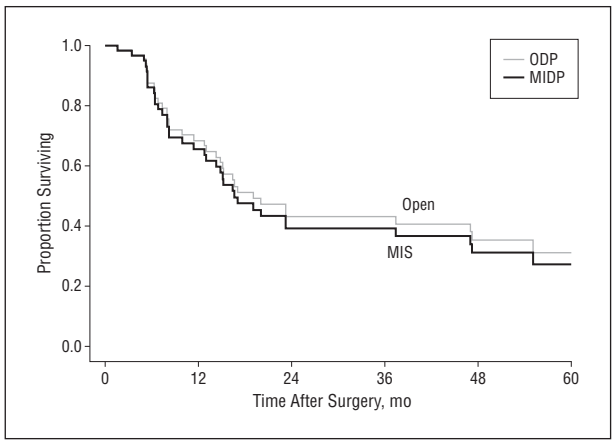


Figure 3. Propensity score–adjusted overall survival analysis after open (ODP) and minimally invasive distal pancreatectomy (MIDP) for pancreatic ductal carcinoma (relative hazard, 1.11 [95% CI, 0.47-2.62]; $P = .80$).

of receiving MIDP increased relative to the base year 2007 as the CCI rose from 0 to 9. We speculate that the perceived benefits of MIDP for patients with medical comorbidities created a selection bias in favor of MIDP during the course of the study. Conversely, ODP was progressively reserved for healthier patients.

SURVIVAL OUTCOMES

Nearly all patients received adjuvant therapy after surgery for PDC (25 [89%] after MIDP and 29 [85%] after ODP; $P = .72$). Of these, 43 (80%) received gemcitabine hydrochloride; 9 (17%), fluorouracil; and 2 (4%), capecitabine. All patients with positive surgical margins received adjuvant chemoradiotherapy with fluorouracil (n = 3) or gemcitabine (n = 5).

Median overall survival (**Figure 2**) for the entire cohort was 19 (95% CI, 14-47) months. Calculation of technique-dependent overall survival was adjusted for the increased propensity to perform MIDP among patients with a higher preoperative CCI and later surgery dates. No differences in propensity-adjusted overall survival were observed between the cohorts (hazard ratio, 1.11 [95% CI, 0.47-2.62]; $P = .80$) (**Figure 3**). The only pathological variable associated with procedure was nodal stage: 57% of the MIDP patients were node positive vs 38% of the ODP patients ($P = .07$). Adjusting the proportional hazards regression for nodal stage in addition to propensity score decreased the hazard ratio from 1.11 to 1.02 (95% CI, 0.44-2.36; $P = .96$), meaning that overall survival was the same after ODP and intended MIDP. We found a trend toward improved overall survival after completed MIDP compared with ODP (hazard ratio, 0.63 [95% CI, 0.21-1.88]; $P = .40$). We detected no evidence of increased risk of local recurrence after MIDP compared with ODP; 2 of 28 patients undergoing MIDP (7%) experienced local recurrence as their sole evidence of progression compared with 1 of 34 patients undergoing ODP (3%) ($P = .59$).

COMMENT

This retrospective study compared clinicopathological and long-term oncologic outcomes after MIDP and ODP for PDC

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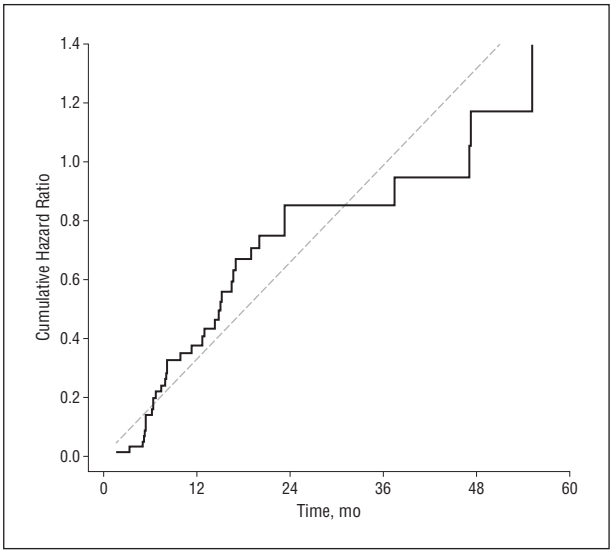


Figure 4. Cumulative hazard ratio of death from pancreatic ductal carcinoma (PDC) as a function of time after surgical resection. The hazard ratio for PDC-related death is highest in the first 8 months and falls rapidly after 24 months despite the provision of adjuvant chemotherapy to 53 study patients (86%). Diagonal line represents a line of constant hazard, or unity.

at a single institution. Intention-to-treat analysis demonstrated no evidence of inferiority of survival after MIDP compared with ODP. Cancer outcomes were independent of surgical technique, with margin-negative outcomes and lymph node clearance similar to those of a large series of ODP.[8] Conversions from intended MIDP to ODP were associated with significantly greater risk of high-grade histologic findings and node positivity, risk factors for cancer death[18] independent of the intended technique of surgical resection. Patients in the MIDP cohort experienced shorter hospital stay and reduced blood loss, with rates and severity of postoperative complications equivalent to ODP. Nearly all patients received adjuvant therapy, and both cohorts had equivalent overall survival after adjusting for the time- and comorbidity-dependent propensity to perform MIDP.

Our study has important limitations, including its retrospective nature, nonrandomized patient selection, influence of surgeon preference, and small sample size. Furthermore, the follow-up after MIDP was necessarily shorter than that after ODP. We addressed the lack of randomization by using a propensity score to adjust for selection biases. Furthermore, we analyzed consecutive patient records from 2002 through 2010 to reduce sampling bias. Nonetheless, we were unable to detect patient or tumor factors contributing to an obvious bias favoring smaller tumors at an earlier stage in the MIDP group. In fact, propensity score analysis identified the opposite: patients with higher CCIs were more likely to undergo MIDP than ODP regardless of age, body mass index, tumor size, or radiographic stage. This likelihood, especially in the latter part of the study, suggests an evolving surgeon bias toward the less physiologically stressful procedure. The odds ratio of undergoing MIDP for PDC increased every year until 8 of 9 cases (89%) were performed with minimal access techniques in the final year (Figure 1). We speculate that systematic analysis of postoperative quality of life would have shown significant benefit to high-risk cancer patients that were apparent to the surgical team in daily practice.

Several studies have compared short-term perioperative outcomes after MIDP and ODP without demonstrating differences sufficiently compelling to outweigh the potential hazards of MIDP for PDC.[1-4,7,8,19-23] Eom and colleagues[7] compared short-term clinical outcomes between patients undergoing LDP or ODP, predominantly for benign distal pancreatic lesions. Although the patients were matched by age, sex, and diagnosis, tumor diameter was larger in the ODP group (6.2 cm) than in the LDP group (4 cm). Hospital stay was shorter after LDP but at a higher overall cost ($4884 vs $3401) owing to instrument expense.[7] The Central Pancreas Consortium subsequently completed the largest study comparing 23 patients undergoing LDP with a matched cohort of 70 undergoing ODP for PDC and specifically analyzed cancer outcomes by intention to treat.[1] They found a trend toward reduced blood loss and hospital length of stay after LDP but no difference in progression-free or overall survival compared with ODP. Subsequent multivariate Cox regression analysis did not identify procedure-specific risk factors for inferior outcomes.

The 2 dominant procedure-specific risks of MIDP for PDC are inferior margin clearance and the perioperative hazard of conversion to ODP. Our data constitute the second set of published outcomes demonstrating equivalent rates of margin-negative resection and lymph node harvest after ODP and MIDP. An objective measure of margin clearance (margin distance) did not demonstrate any evidence of inferior soft-tissue clearance based on surgical technique. The resulting median overall survival of the entire cohort was 19 months, with overlapping survival curves for the ODP and MIDP groups after correcting for the propensity to perform MIDP. These findings mirror data reported by Kooby et al[1] and prior series of ODP.[24,25] In fact, the cumulative hazard rate for death from PDC at the University of Pittsburgh Medical Center improved significantly during the 9-year study despite increased propensity to perform MIDP (data not shown). The reduction in the relative risk for PDC-related death was approximately 25% by 2010, with a linear decline every year after 2002.

Although preoperative cancer antigen 19-9 levels were not measured for 22 of 62 patients (35%) in this study, the effects of levels exceeding 1000 U/mL (conversion to kilounits per liter is 1:1) on survival were far more deleterious than small differences due to surgical technique. A cancer antigen 19-9 level greater than 1000 U/mL was associated with a relative risk of 7.8 for PDC death among the 7 affected patients ($P < .001$). Excluding these 7 patients by improved preoperative staging would have increased median survival to longer than 35 months for the entire cohort, demonstrating the greater effect that undetected metastases have on survival compared with surgical technique. Early postoperative recurrence and death at 4 to 10 postoperative months were reflected in the accelerating cumulative hazard in **Figure 4** and signify the dominant role of tumor biological factors in outcome.

Although our data demonstrate no evidence that MIDP is inferior to ODP, selection bias limits generalizability to other centers. Given the complexity of this disease, a randomized clinical trial comparing MIDP with ODP might not

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be possible. Noninferiority analysis of our data suggests that an accrual target of 290 patients in 3 years is needed to detect a 40% difference, a realistic target substantially lower than previous estimates.[26] The compelling reason to pursue a national trial is the need to evaluate quality of life after MIDP and ODP in the context of evidence that 71.4% of American patients currently forgo potentially curative treatment for stage I PDC in this modern era.[5]

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