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ORIGINAL ARTICLE

Perioperative and oncologic outcomes of open, laparoscopic, and robotic distal pancreatectomy for pancreatic adenocarcinoma

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Abstract

The utilization of minimally invasive distal pancreatectomy (MIDP) is increasing, yet debate remains regarding its oncologic safety in the setting of pancreatic adenocarcinoma (PDAC). Herein we present our institutional experience with robotic (RDP), laparoscopic (LDP), and open distal pancreatectomy (ODP) in the setting of PDAC.

Retrospective review of a prospectively collected single institutional database of patients undergoing consecutive ODP, LDP, and RDP for left-sided PDAC between January 2008 and December 2019 at the University of Pittsburgh Medical Center (UPMC) was done. Perioperative and postoperative outcomes were compared using non-parametric testing and Fischer exact or chi-squared testing. Kaplan–Meier survival curves for disease-free survival and overall survival were compared by Log-Rank sum test. Backward Cox-proportional hazard regression analysis was used to determine if the operative approach was an independent predictor of recurrence and overall survival.

Over 12 years, 146 consecutive distal pancreatectomies for PDAC were performed, of which 28.1% ODP, 60.3% RDP, and 11.6% LDP. There were no statistical differences in patients' baseline characteristics, including gender, comorbidities, prior abdominal surgeries, and AJCC^{8th} stage ($p > 0.05$). Postoperatively, there was no difference in the frequency of major complications ($p = 0.414$), CR-POPF ($p = 0.563$), or DGE ($p = 0.179$). The median overall survival was 28.4 months for ODP, 34.6 months for RDP, and 32.5 months for LDP (Log Rank $p = 0.914$). On multivariate Cox proportional hazard analysis, the surgical approach was not associated with overall survival. This comparative analysis suggests a non-inferiority of RDP platforms, compared to LDP and classic ODP. The merits of MIS pancreatic surgery in the setting of PDAC should be evaluated in future prospective studies with care to analyze RDP outcomes separately from LDP.

Keywords Distal pancreatectomy · Minimally invasive pancreatectomy · Robotic distal pancreatectomy · Pancreatic cancer

Introduction

Pancreatic surgery represents one of the most technically demanding abdominal procedures. During the last five decades, several advancements in surgical techniques, the introduction of new surgical platforms and a greater understanding of the biology of the various pancreatic lesions have led to a rapid expansion of the indications and modalities of pancreatic surgery [1–4]. The utilization of minimally invasive distal pancreatectomy (MIDP) is increasing, and several retrospective studies, metanalysis and one published randomized controlled trial reported on its safety and feasibility in mixed cohorts of benign and malignant pancreatic disease [5–8]. Nevertheless, debate remains regarding MIDP oncologic safety in the setting of pancreatic adenocarcinoma (PDAC) [9, 10]. The DIPLOMA study, a pan-European propensity score matched study, demonstrated comparable survival after MIDP and ODP for PDAC [5]. Nonetheless, van Hilst and al. observed a lower rate of lymph node retrieval and Gerota's fascia resection in the MIDP compared to the ODP. Importantly, in this study, the cohort of MIDP (356 cases) was chiefly represented by laparoscopic DP (LDP), while the robotic-assisted (RDP) cohort consisted of only a minority of cases (4%) [5].

In a recent meta-analysis, Zhou et al. conducted a comprehensive evaluation of RDP compared to ODP including seven studies conducted at high-volume robotic surgery

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centers and demonstrated an advantage for the former in terms of lower estimated blood loss and lower postoperative mortality rates without any major differences for operating time, number of lymph nodes harvested, positive margin rate, spleen preservation rate and severe morbidity rate between the two groups. [11] However, the studies selected in the meta-analysis by Zhou et al. reported on a mixed cohort of patients with benign and malignant pancreatic disease alike. [11] Therefore, a conclusion on the benefits and drawbacks of RDP compared to ODP in the setting of PDAC cannot be reached. Herein we present our institutional experience with RDP, LDP, and ODP in the setting of distal pancreatic adenocarcinoma and evaluate differences in perioperative and postoperative outcomes.

Methods

Retrospective review of a prospectively collected single institutional database of patients undergoing consecutive ODP, LDP, and RDP for left-sided PDAC between January 2008 and December 2019 at the University of Pittsburgh Medical Center (UPMC). Lesions classified preoperatively as T4 based on American Joint Committee on Cancer (AJCC) 8th edition [12] were excluded from the analysis to allow for a more homogeneous group of distal pancreatic adenocarcinoma and minimize the contamination with patients that required multivisceral resection. The study was approved by the University of Pittsburgh's institutional review board. Procedures were performed by 15 surgeons, most with specialized training in pancreatic surgery, yet over 85% of cases were performed by four surgeons. UPMC is a high-volume center for pancreatic surgery—as evidenced by 2159 pancreatic resections during the study period (including pancreatoduodenectomy, distal pancreatectomy, Appleby procedure, total pancreatectomy, central pancreatectomy, and enucleation, with pancreatoduodenectomy accounting for 64.1%). Moreover, UPMC is recognized as a high-volume center for pancreatic adenocarcinoma resection—evidenced by 950 resections performed during the study period, among which 75.8% were pancreatoduodenectomies.

RDPs were performed by four surgeons with specialized training in robotic pancreatic surgery. Selection of operative technique is non-randomized and at the discretion of the surgeon. Analysis was performed on an intention-to-treat basis (all conversions were included in the laparoscopic or robotic groups).

Preoperative, operative, postoperative, and oncologic factors are collected in the database by a dedicated database manager. Neoadjuvant therapy (NAT) refers to any cancer-specific treatment (i.e., systemic chemotherapy or chemoradiotherapy) administered prior to surgical resection. It is our practice to offer NAT to patients with resectable as well as borderline resectable disease; the decision to administer NAT is based on a number of factors in addition to the clinical stage, including patient functional status, availability of NAT trials, and patient preference. NAT was recorded as either neoadjuvant chemotherapy (NAC; where patients received only systemic therapy preoperatively) or neoadjuvant chemo-radiotherapy (NCRT; where patients received systemic chemotherapy and local radiotherapy prior to resection). All patients with PDAC are considered for adjuvant therapy—however, some patients fail to receive adjuvant therapy due to post-operative morbidity, poor functional status, and unwillingness to continue treatment. All systemic therapy administered after surgery, prior to recurrence is considered adjuvant, while systemic therapy administered after development of recurrence is recorded as salvage therapy.

Negative margin resection was defined as tumor distance from the closest margin > 1 mm. Operative time was calculated from first incision to closure of last incision and taken from the intraoperative nursing record. Pancreatic fistula was graded according to the International Study Group on Pancreatic Fistula (ISGPF) classification. Postoperative complications were assessed by the Clavien-Dindo score with the worst complication used to grade overall severity. Readmission was defined as any inpatient hospitalization. Perioperative mortality was defined as death within 30 days or during the index hospitalization after surgery. Data were tested for normalcy and reported with mean and standard deviation (SD). Non-parametric testing was used for all variables without a normal distribution and reported with a median and interquartile range (IQR). Fischer exact or chi-squared testing was used for all categorical variables, and proportions were reported. Survival analysis, including DFS and OS, was performed using Kaplan–Meier survival curves compared by log-rank sum test. Backward Cox-proportional hazard regression analysis was performed to determine if the operative approach was an independent predictor of recurrence and overall survival. Only statistically significant variables were included in the final model. Statistical analysis was performed using SPSS version 26, and all statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Over 12 years, a total of 146 consecutive distal pancreatectomies for PDAC were performed, of which 28.1% were ODP, 60.3% were RDP, and 11.6% were LDP. There were no statistical differences in patient demographics, including gender, comorbidities, and prior abdominal surgeries (Table 1).

Table 1 Demographics and treatment variables

Variable	Open ($n=41$)	Robotic ($n=88$)	Laparoscopic ($n=17$)	p-value
Female gender	25 (61.0%)	46 (52.3%)	10 (58.8%)	0.624
Co-morbidity	33 (80.5%)	77 (87.5%)	15 (88.2%)	0.542
DM	9 (22.0%)	32 (36.4%)	4 (23.5%)	0.201
CVD	19 (46.3%)	54 (61.4%)	10 (58.8%)	0.272
ASA				
2	3 (7.3%)	11 (12.6%)	3 (17.6%)	0.757
3	34 (82.9%)	66 (75.9%)	13 (76.5%)	
4	4 (9.8%)	10 (11.5%)	1 (5.9%)	
Prior Abdominal surgery	25 (61.0%)	58 (65.9%)	11 (64.7%)	0.862
Neoadjuvant chemotherapy	18 (43.9%)	42 (47.7%)	4 (23.5%)	0.184
Neoadjuvant radiotherapy	6 (14.6%)	4 (4.5%)	0 (0.0%)	0.053
NAT				
NAC	12 (29.3%)	38 (43.2%)	4 (23.5%)	0.053
NCRT	6 (14.6%)	4 (4.5%)	0 (0.0%)	
Vascular resection	10 (24.4%)	6 (6.8%)	0 (0.0%)	0.004
Conversion	N/A	2 (2.3%)	4 (23.5%)	< 0.001

All values represented as n (%). p-value < 0.05 was considered significant; tested by Chi-square test

DM diabetes mellitus, *CVD* cardiovascular disease, *ASA* American society anesthetists' score, *NAT* neoadjuvant therapy, *NAC* neoadjuvant chemotherapy, *NCRT* neoadjuvant chemoradiotherapy

A significant number of patients underwent neoadjuvant chemotherapy (43.9% ODP, 47.7% RDP and 23.5% LDP, $p=0.184$). On the other hand, a small cohort of patients underwent neoadjuvant radiation (14.6% ODP, 4.5% RDP and 0% LDP, $p=0.053$; Table 1).

Patients in the ODP cohort were more likely to have vascular resection (24.4%) compared to RDP (6.8%) or LDP (0%, $p=0.004$; Table 1). The estimated blood loss (EBL) was lower in the RDP compared to LDP and ODP, although this did not reach statistical significance ($p=0.119$). Remarkably, the RDP group had the lowest median operative time among the three groups (RDP = 213 min, LDP = 238 min, ODP = 348 min; $p<0.001$). Finally, robotic surgery was associated with a lower conversion rate (2.3%) compared to laparoscopic surgery (23.5%, $p<0.001$; Table 1). Pathologically, there was no difference in the percentage of AJCC stage, T stage, N stage, LN positivity, lymphovascular invasion, perineural invasion, and positive margin between the three groups (Table 2). The majority of patients received adjuvant therapy (70.7% for ODP, 71.6% for RDP, and 82.4% for LDP, $p=0.628$; Table 2).

Postoperatively, there was no difference in the frequency of major complications (19.5% for ODP, 15.9% for RDP and 29.4% for LDP, $p=0.414$), CR-POPF (9.8% for ODP, 9.1% for RDP and 17.6% for LDP, $p=0.563$) or DGE (9.8% for ODP, 3.4% for RDP and 0% for LDP, $p=0.179$). A higher rate of postoperative bleeding and reoperation was observed in the LDP cohort compared to the two others, but there was no difference in 90-day mortality among the three groups (Table 3).

The median follow-up for the entire cohort was 32.7 months. The median overall survival was 28.4 months for ODP, 34.6 months for RDP, and 32.5 months for LDP (Log Rank $p=0.914$; Fig. 1 and Table 4). The median progression-free survival was 16.9 months for ODP, 16.6 months for RDP, and 18.8 months for LDP (Log Rank $p=0.681$; Fig. 2 and Table 4). On multivariate Cox proportional hazard analysis, the operative approach was not associated with overall survival (Table 5). Factors associated with worse survival were the presence of comorbidities, lymphovascular invasion, and stage III disease. The receipt of neoadjuvant therapy was associated with improved survival in this unmatched retrospective cohort.

Discussion

The overall safety of left-sided pancreatic surgery has increased tremendously compared to the early reports of the twentieth century [13, 14]. Yet, the introduction of minimally invasive pancreatic surgery during the 1990s has generated much debate, and many remain skeptical of its merit, especially in the setting of pancreatic ductal adenocarcinoma [5, 9]. The current study describes the perioperative and oncologic outcomes for open, laparoscopic, and robotic distal pancreatectomy for PDAC performed at UPMC between 2008 and 2019.

Our cohort is heavily biased toward MIS techniques, and over 60% of cases were performed using the robotic platform. It must be noted that LDP has been largely abandoned

Table 2 Pathological and Oncological outcomes

Variable	Open ($n=41$)	Robotic ($n=88$)	Laparoscopic ($n=17$)	p-value
AJCC^{8th} stage				
1	11 (26.8%)	29 (33.0%)	5 (29.4%)	0.523
2	25 (61.0%)	40 (45.5%)	8 (47.1%)	
3	5 (12.2%)	19 (21.6%)	4 (23.5%)	
T-stage				
T1a	3 (7.3%)	3 (3.4%)	0 (0.0%)	0.717
T1b	2 (4.9%)	3 (3.4%)	0 (0.0%)	
T1c	8 (19.5%)	12 (13.6%)	3 (17.6%)	
T2	14 (34.1%)	47 (53.4%)	9 (52.9%)	
T3	14 (34.1%)	22 (25.0%)	5 (29.4%)	
Tx	0 (0.0%)	1 (1.1%)	0 (0.0%)	
N-stage				
N0	14 (34.1%)	37 (42.0%)	8 (47.1%)	0.216
N1	22 (53.7%)	30 (34.1%)	5 (29.4%)	
N2	5 (12.2%)	21 (23.9%)	4 (23.5%)	
LN positivity	27 (65.9%)	51 (58.0%)	9 (52.9%)	0.583
LN retrieved*	20 (9–48)	27 (10–56)	21 (12–37)	0.077
Grade				
G1	1 (2.4%)	0 (0.0%)	1 (5.9%)	0.148
G2	30 (73.2%)	73 (83.0%)	11 (64.7%)	
G3	9 (22.0%)	10 (11.4%)	5 (29.4%)	
G4	0 (0.0%)	2 (2.3%)	0 (0.0%)	
LVI	29 (70.7%)	61 (70.9%)	10 (62.5%)	0.789
PNI	34 (82.9%)	73 (83.9%)	17 (100%)	0.194
R1 margin	14 (34.1%)	33 (37.5%)	4 (23.5%)	0.538
Adjuvant therapy	29 (70.7%)	63 (71.6%)	14 (82.4%)	0.628
Recurrence	22 (55.0%)	54 (62.1%)	9 (52.9%)	0.65
Surgical bed recurrence	13 (32.5%)	33 (37.9%)	4 (23.5%)	0.491
Systemic recurrence	21 (52.5%)	50 (57.5%)	8 (47.1%)	0.688
Salvage therapy	15 (36.6%)	44 (50.0%)	7 (41.2%)	0.41
Death	24 (58.5%)	50 (56.8%)	12 (70.6%)	0.571

All values represented as n (%). p-value < 0.05 was considered significant; tested by Chi-square test

AJCC American joint committee on cancer, *T* tumor, *N* nodal stage, *LN* lymph node, *G* grade, *LVI* lympho-vascular invasion, *PNI* Perineural invasion, *R1* Defined as a microscopic radical resection with a distance between the tumor and the margin of < 1 mm

at our institution following the introduction of RDP as institutional data demonstrated superiority of outcomes for RDP compared to LDP in a mixed cohort of benign and malignant diseases. [3, 15, 16] Moreover, a comprehensive comparative analysis of cost-effectiveness and perioperative outcomes between MIS platforms and classic ODP demonstrated superiority of the RDP compared to both ODP and LDP in a mixed cohort of benign and malignant pancreatic disease, these data have been previously published. [17]

In the current intention-to-treat analysis, we found no evidence of inferiority of survival after RDP compared to LDP and ODP performed specifically for PDAC. All cancer-related outcomes remained independent of surgical technique, with margin-negative resection and lymph node harvest similar to previously reported series. RDP was associated with a lower conversion rate than LDP, although the LDP represented only a small portion of our cohort. [18] The decreased conversion rate is at least partly explained by the increased instrument dexterity offered by the robotic platform and the enhanced three-dimensional vision, which are valuable additions to the lack of versatility of the classic laparoscopic instrumentation. As a result, tissue dissection is facilitated, especially in the setting of malignant disease when classic surgical planes are distorted by direct tumor invasion or desmoplastic reaction. Yet, the most common reasons for conversion in both groups included elevated BMI, intraoperative bleeding, tumor proximity to major vasculature, and surgeon experience.

Nonetheless, the majority of vascular resections were still preferentially performed in the ODP group compared to the

Table 3 Post-operative outcomes

Variable	Open ($n=41$)	Robotic ($n=88$)	Laparoscopic ($n=17$)	p-value
Clavien = / > 3	8 (19.5%)	14 (15.9%)	5 (29.4%)	0.414
Clavien				
0	12 (29.3%)	24 (27.3%)	3 (17.6%)	0.524
1	12 (29.3%)	17 (19.3%)	5 (29.4%)	
2	9 (22.0%)	33 (37.5%)	4 (23.5%)	
3	4 (9.8%)	8 (9.1%)	2 (11.8%)	
4	3 (7.3%)	4 (4.5%)	1 (5.9%)	
5	1 (2.4%)	2 (2.3%)	2 (11.8%)	
Operative time (min)	248 (181–334)	213 (174–241)	348 (232–416)	0.001
EBL (mL)	200 (100–450)	150 (50–200)	212 (50–606)	0.119
Complication (< 90 days)	29 (70.7%)	64 (72.7%)	14 (82.4%)	0.649
CR-POPF	4 (9.8%)	8 (9.1%)	3 (17.6%)	0.563
Wound infection	4 (9.8%)	4 (4.5%)	0 (0.0%)	0.275
DGE	4 (9.8%)	3 (3.4%)	0 (0.0%)	0.179
GI Bleed	1 (2.4%)	2 (2.3%)	1 (5.9%)	0.690
Re-operation (< 90 days)	3 (7.3%)	2 (2.3%)	3 (17.6%)	0.032
Length of stay (days)	7 (5.5–7)	5 (5–7)	7 (5–8)	0.695
30-day mortality	1 (2.4%)	0 (0.0%)	1 (5.9%)	0.127
90-day mortality	1 (2.4%)	2 (2.3%)	2 (11.8%)	0.132

All values represented as n (%). p-value < 0.05 was considered significant; tested by Chi-square test

CR-POPF clinically relevant post-operative pancreatic fistula, *DGE* delayed gastric emptying, *GI* gastrointestinal

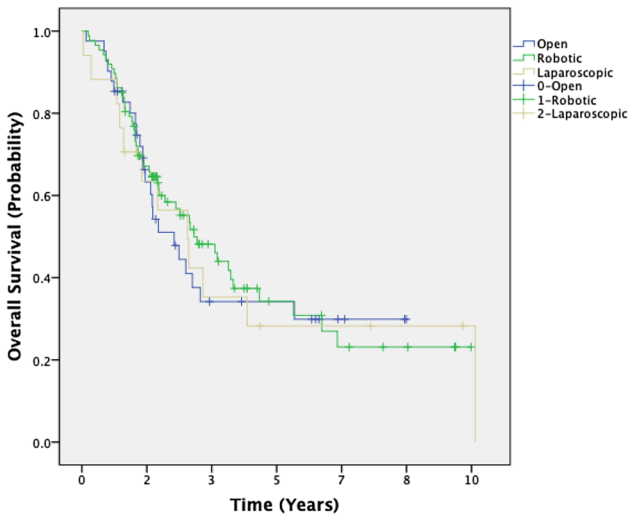

Fig. 1 Median overall survival for all patients undergoing open (ODP), robotic (RDP) and laparoscopic (LDP) distal pancreatectomy for adenocarcinoma. Median OS from the time of diagnosis for the entire cohort of resected distal PDAC: mOS = 32.9 months (IQR 27.1–38.6); Open: mOS = 28.4 (IQR 17.7–39.1); Robotic: mOS = 34.6 (IQR 22.7–45.4); Laparoscopic: mOS 32.5 (IQR 15.5–49.5) Log-rank $p = 0.914$

RDP, and none was performed in the LDP. When considering a MIDP approach for a PDAC with mesenteric venous involvement, it is paramount to ascertain the extension of venous involvement and anticipate the necessity for segmental venous resection rather than a more conservative partial venous resection. It has been our preference to proceed with ODP when the need for a segmental venous resection is anticipated based on preoperative imaging.

Although our group and others have previously described the safety and feasibility of robotic-assisted distal pancreatectomy with celiac axis resection, this procedure is technically demanding, especially in the setting of concomitant portal vein (PV) or superior mesenteric vein involvement (SMV) [19–21]. In the setting of PDAC, when both the celiac axis and the PV or the SMV are involved, an open approach might be preferable to facilitate vascular dissection and reconstruction.

Neoadjuvant chemotherapy (NAT) was utilized in nearly half of the entire cohort without significant differences between the ODP and RDP. No consensus on the role of NAT for left-sided PDAC currently exists in the literature [22]. At our institution, the use of NAT in distal PDAC has evolved during the study period, and most recently, NAT is offered to all patients with acceptable performance status (ECOG 0–1) based on multidisciplinary consensus and eligibility for clinical trials.

Postoperative major complications rates were similar between the groups, although the LDP cohorts had an overall higher rate of complications, which did not reach statistical significance. The major complication and

Table 4 Overall survival of patients with pancreatic ductal adenocarcinoma stratified by operative treatment

Treatment	Median survival* (months)	Log-rank analysis *p*-value	Progression free* survival (months)	Log-rank analysis *p*-value
Open	28.4 (17.7–39.1)	0.914	16.9 (14.2–19.7)	0.681
Robotic	34.6 (22.7–45.4)		16.6 (12.4–20.8)	
Laparoscopic	32.5 (15.5–49.5)		18.8 (4.2–33.5)	

*Median and interquartile range

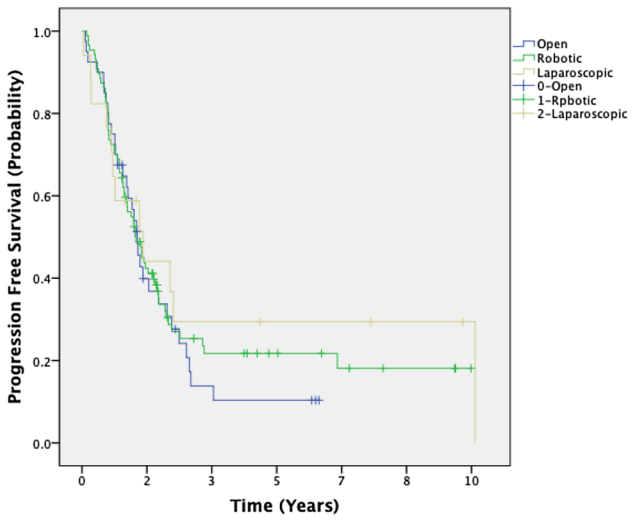

Fig. 2 Progression free survival for all patients undergoing open (ODP), robotic (RDP) and laparoscopic (LDP) distal pancreatectomy for adenocarcinoma. Median PFS from the time of diagnosis for the entire cohort of resected distal PDAC: mPFS = 16.9 months (IQR 14.7–19.1); Open: mPFS = 16.9 months (IQR 14.2–19.7); Robotic: mPFS = 16.6 (IQR 12.5–20.8); Laparoscopic: 18.8 (4.2–33.5); Log-rank = 0.681

Table 5 Cox-proportional hazard regression analysis for overall survival

Variable	Hazard ratio	95% CI	*p*-value
NAT	0.535	0.335–0.855	0.009
CCI age adjusted	1.167	1.044–1.304	0.007
AJCC 8th (I = Reference)			
Stage II	1.229	0.664–2.273	0.512
Stage III	2.157	1.064–4.375	0.033
LVI	2.820	1.427–5.571	0.003
Adjuvant chemotherapy	0.491	0.297–0.812	0.006

NAT neoadjuvant therapy, *AJCC* American joint committee on cancer, *LVI* lymphovascular invasion

reoperation rates for the LDP—recorded in this series—are higher than what was reported by our institution before the introduction of RDP, these results are at least partially biased by the small sample size in the current series. [16]

An important observation is the high rate of adjuvant therapy administration in all three cohorts ODP, RDP, and LDP, which occurred in over 70% of cases. Candidacy for adjuvant therapy is commonly predicated on overall patient performance status and satisfactory recovery from the surgical procedure [23]. The overall rate of adjuvant therapy in this study is encouraging and echoes the rate reported in the literature suggesting non-inferiority of minimally invasive platforms compared to ODP [22].

Ultimately, overall survival was similar between the three groups and comparable with published reports from high-volume pancreatic cancer centers [5]. Although this is an unmatched cohort analyzing three different surgical techniques, we attempted to control for major confounding factors in our Cox model. The outcomes obtained in the RDP group suggest a valuable role for this surgical modality, even in the setting of PDAC.

This analysis has several important limitations. First, as a retrospective study, it is subject to the inherent bias of this study design. Second, a significant portion of the ODP cohort underwent vascular resection in a disproportional ratio compared to RDP and LDP. Most of the vascular resections involved the PV/SMV vessels and were done for centrally located pancreatic lesions. Therefore, at least a portion of the ODP group underwent more extensive surgery than the RDP and LDP. Third, the limited number of LDP included in this study hinders the conclusions derived from the comparison of LDP with RDP and ODP in both the univariate and Cox model. Fourth, the NAT regimens and selection criteria evolved during the study period, and no definitive conclusion can be made on the role of NAT in distal PDAC. Fifth, the exclusion of T4 lesions (AJCC^{8th})—as an attempt to limit contamination from very large tumors requiring multivisceral resection—limits the generalizability of this study.

In conclusion, this limited institutional series suggests that RDP is safe and feasible in well-selected left-sided PDAC when performed by experienced pancreatic surgeons in a high-volume pancreatic center. Moreover, RDP was not inferior to ODP and LDP in oncology-specific outcomes and overall survival. Further studies evaluating the merits of MIS pancreatic surgery for PDAC should strive to separate the robotic platform from the purely laparoscopic-assisted

technique as a growing body of evidence suggests that more favorable outcomes are associated with RDP compared to LDP.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights Retrospective chart reviews qualify for "exempt" status under human subjects regulations.

Informed consent Consent requirement was waived as this was a retrospective chart review study.

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