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The Current State of Minimally Invasive Distal Pancreatectomy

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Abstract Since its advent nearly 15 years ago, minimally invasive distal pancreatectomy has gradually increased in popularity. Numerous reports have now documented the safety and feasibility of the laparoscopic approach to left-sided pancreas resections, and large-scale comparisons have been made between the laparoscopic and open approaches regarding perioperative outcomes for both benign and malignant lesions. Furthermore, several high-volume centers have described their initial experiences with robotic distal pancreatectomy in comparison with laparoscopic and open resections. This review summarizes the literature for both laparoscopic and robotic distal pancreatectomy over the past year, highlighting novel advances. Although studies suggest that minimally invasive distal pancreatectomy is equivalent if not superior to the open approach in some respects, randomized studies are needed to best delineate the putative benefits.

Keywords Laparoscopy · Robotic · Minimally invasive · Distal pancreatectomy · Comparative · Pancreas resection · Pancreatic cancer · Spleen-preserving · Preoperative factors · Malignancy

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Introduction

Distal pancreatectomy for the resection of left-sided pancreatic lesions has been performed since the early twentieth century [1]. Compared with pancreatoduodenectomy, the lack of technically challenging anastomoses makes left-sided resection better suited for the application of minimally invasive approaches. Laparoscopic distal pancreatectomy (LDP) was first described approximately 15 years ago [2, 3]. The approach has several potential technical advantages over open resection, including better visualization and exposure of the pancreas within the retroperitoneum. Since its inception, multiple studies have documented the safety and feasibility of the laparoscopic approach [4–17], and several reports have chronicled initial experiences with robotic distal pancreatectomy (RDP) as well [18–20]. Minimally invasive distal pancreatectomy (MIDP; encompassing LDP and RDP) is steadily becoming more widespread, and with accrued experience, increasingly complex lesions are being approached. As a result, large-scale studies have emerged comparing intraoperative, postoperative, and oncologic outcomes with MIDP versus open distal pancreatectomy (ODP). This review aims to summarize the literature for MIDP over the past year, highlighting significant recent advances.

Meta-analyses Comparing Laparoscopic and Open Distal Pancreatectomy

The feasibility of laparoscopic pancreatic surgery was first documented in numerous case series largely conducted at single institutions [4–17]. As familiarity developed, significant experiences were reported. Naturally, higher-volume centers have offered direct comparisons of laparoscopic and open outcomes [6, 7, 11, 14, 16, 21–27]. Over the past year,

five reports have advanced this literature by pooling such studies using meta-analytical techniques [28, 29•, 30, 31, 32•]. These represent the most comprehensive evidence to date comparing LDP and ODP.

Nigri et al. [30] performed the first meta-analysis comparing these approaches, noting no significant difference in operating time, mortality, or reoperation rates between the minimally invasive and open groups. Patients undergoing LDP had significantly less blood loss, required fewer transfusions, and had a higher rate of splenic preservation. Fewer overall complications, major complications, surgical site infections, and pancreatic fistulas were noted in the laparoscopic group, and length of stay was significantly shorter. These findings were largely confirmed in a subsequent meta-analysis by Jusoh and Ammori [31], except that there was no significant difference in the overall pancreatic fistula rate. Xie et al. [28] published slightly different results. In their analysis, the operating time for open resections was significantly shorter than for laparoscopic resections, and the rates of pancreatic fistula and overall morbidity did not differ between groups. Variability in these results may be accounted for by differences in the actual studies included.

Since use of MIDP has grown exponentially of late, the two most recent meta-analyses are the most robust. Venkat et al. [29•] have provided the meta-analysis with the largest number of patients. They identified 18 studies through January 2011 that fulfilled the selection criteria; 773 patients who underwent LDP and 1,041 who underwent ODP were included. Mean operating time was slightly but not significantly greater for the laparoscopic group, whereas blood loss was significantly lower in the laparoscopic group (difference of 355 ml) along with lower odds of blood transfusion (odds ratio 0.23, $P = 0.01$). Postoperatively, the laparoscopic group had significantly shorter time to oral intake as well as a shorter duration of hospitalization (difference of 4.1 days). Overall morbidity was lower in the laparoscopic group (33.9 vs 44.2 %), with a significant reduction in surgical site infections. However, major complication rates, reoperation rates, pancreatic fistula rates, and mortality did not significantly differ between the two groups. There was a significantly lower incidence of readmission for the laparoscopic group, although only three of the studies reported this outcome. Subgroup analyses altered the statistical significance for a few parameters (operating time, transfusion rates), but outcomes such as overall complications, pancreatic fistulae, readmissions, and mortality remained unchanged.

More recently, Jin et al. [32•] pooled 15 studies taken from all available reports through April 2012. A total of 561 LDP and 895 ODP were included in these reports. There was no significant difference in operating time, although in the pooled analysis there was a trend toward shorter operating time in the ODP group. Intraoperative blood loss was significantly lower in the laparoscopic group, with fewer patients requiring blood transfusion (odds ratio 0.28, $P = 0.01$). As has been noted elsewhere, the rate of splenic preservation was significantly higher in the laparoscopic group (odds ratio 2.98, $P < 0.00001$). Postoperatively, the laparoscopic cohort had a shorter length of stay and fewer surgical site infections, but there was no difference in the rate of clinically significant pancreatic fistula (grade B/C by International Study Group for Pancreatic Fistula, ISGPF, standards [33]) or any other complication. Rates of reoperation and readmission did not differ. Overall morbidity and complication rates were not calculated in this study since the criteria used to define these measures were not comparable between studies. Subgroup analysis including only those studies deemed to be high quality showed the time to first flatus to be significantly shorter but did not change the analysis for any other outcome.

In aggregate, these studies most consistently demonstrate that LDP minimizes blood loss, shortens length of stay, and promotes splenic preservation, whereas complications in this setting may not differ. Unfortunately, all of these meta-analyses suffer from similar flaws that were in many cases acknowledged. All included studies were retrospective series, and there was undoubtedly selection bias from the outset. Only one meta-analysis [31] reported a quantitative difference in the size of the tumors resected, but it is exceedingly likely that far distal lesions, smaller tumors, and nonmalignant lesions were more often approached laparoscopically—especially in the early era. Furthermore, critical results such as major complication rates and pancreatic fistula rates are difficult to interpret in that their definitions differed across studies—validated and accepted systems such as the Clavien–Dindo classification for major complications [34] or the ISGPF definition for pancreatic fistula were not uniformly employed. These shortcomings highlight the need for randomized prospective studies using standardized definitions of postoperative outcomes.

Open Versus Laparoscopic Pancreatectomy: Identification of Preoperative Factors Suggesting a Preferred Approach

Although retrospective studies suggest equivalence or perhaps superiority of LDP versus ODP for common outcomes, it is plausible that certain groups of patients might benefit from one approach over the other. One might expect from a technical standpoint that patients with larger, more central lesions benefit more from open surgery than those with smaller, distal lesions. However, guidelines recommending which patients should undergo LDP versus ODP do not yet exist. There has been one recent attempt to delineate these indications. Cho et al. [35••] through a multi-institutional effort assessed whether risk factors for adverse postoperative outcomes

existed and differed between ODP and LDP. Adverse outcomes in this report were defined as clinically significant pancreatic fistulae (by ISGPF criteria) and complications defined as major based on a previously described scoring system [36].

On multivariate analysis, risk factors for major complications and pancreatic fistulae differed for the two approaches. Specifically, risk factors for major complication after ODP were splenic preservation and nonstapled pancreatic parenchymal transection, whereas no such risk factors were identified for LDP. Risk factors for clinically significant pancreatic fistulae after ODP were splenic preservation and prolonged operating time, whereas risk factors for fistulae after LDP were obesity (BMI $>$ 27) and long specimen length (more than 8.5 cm). The group then compared matched cohorts to define subgroups of patients whose clinical outcome might differ depending on the operative approach. Patients undergoing splenic preservation were more likely to develop major complications after ODP than after LDP, whereas patients undergoing splenic preservation, nonobese patients, patients without adenocarcinoma diagnoses, and patients with peripherally located tumors were more likely to develop clinically significant pancreatic fistulae after ODP than after LDP. Of these parameters, the latter three can be evaluated preoperatively. For patients who met all three of these criteria, the likelihood of significant pancreatic fistula was 14.1 % after ODP versus 1.7 % after LDP. Notably, no parameter was identified for which major complications or clinically significant fistulae were more likely after LDP than after ODP.

These investigators noted selection bias in that nonobese patients, those with peripherally located tumors, and those without adenocarcinoma are better candidates for laparoscopic resection. Thus, patients in these groups who undergo ODP likely have nonmeasured variables that render them more prone to complications. Likewise, patients with pancreatitis, adenocarcinoma, and larger, more centrally located tumors more often underwent open resection in this series. Thus, candidates with these features who had LDP may not represent the group as a whole. Nonetheless, it remains noteworthy that no variable was identified for which adverse outcomes were commoner in the laparoscopic group. These data again suggest that LDP is at least equivalent to ODP with regard to oncologic outcomes and furthermore identify patients likely to benefit most from laparoscopic versus open resection. However, they again emphasize the need for prospective, randomized studies to directly compare outcomes.

Laparoscopic Versus Open Distal Pancreatectomy for Malignant Lesions

To this point, LDP has gained widespread acceptance largely in the setting of benign or premalignant lesions. With the advent of LDP, most investigators were reticent to approach cases of malignant lesions for fear of compromising oncologic principles. Over time, increasing application of MIDP has yielded sizable cohorts of resected carcinomas. These have been detailed in numerous studies although sample sizes have generally been small and reports have usually been derived from single institutions [37, 38].

Kooby et al. [39] were the first to perform a multicenter comparative analysis of LDP versus ODP for pancreatic ductal adenocarcinoma in a matched cohort of patients: 10.8 % of patients underwent LDP and 89.2 % were resected in open fashion. Conversions to ODP (17 %) were included in the laparoscopic group to maintain an intent-to-treat analysis. Kooby et al. found no difference in the rates of positive resection margins, the number of nodes examined, and overall survival, although median follow-up was only 10 months. The method of resection was not independently associated with worse survival. They concluded that the laparoscopic approach was suitable in the setting of pancreatic ductal adenocarcinoma yet acknowledged that median follow-up was relatively short. For a larger comparison, the meta-analysis of Venkat et al. [29•] pooled four studies that reported margin status and lymph node harvests. There was no significant difference between minimally invasive and open resection with respect to positive margins, and the number of lymph nodes harvested was similar in three of the four studies that reported lymph node counts. These results again suggest that LDP may be comparable to ODP with regard to oncologic outcomes.

Retrospective studies used to compare oncologic outcomes for LDP versus ODP are inherently limited by selection bias. Randomized trials would eliminate such bias, as would a uniform approach to all resections. Marangos et al. [40•] recently contributed a single-institution, retrospective study of prospectively collected data detailing their experience with LDP for malignant lesions. Their practice has been to remove all distal pancreatic lesions laparoscopically; they cite fewer than five ODP at their institution over the past 15 years. This largely eliminates selection bias. Thirty of their 250 consecutive patients undergoing laparoscopic resection had a histologically confirmed diagnosis of exocrine pancreatic cancer. They reported an outstanding 93 % rate of R0 resections in the laparoscopic setting. The number of lymph nodes retrieved (average of five) was relatively low compared with the numbers in other reports in the literature [38, 39]. However, this did not appear to have a significant effect on overall survival—median survival after laparoscopic resection was 23 months for patients with exocrine carcinoma and 19 months for patients with ductal adenocarcinoma specifically. The 3-year survival rate for patients with ductal adenocarcinoma was 30 %. These results are comparable with published results for open

resection [41]. Data presented in this study thus support the notion that laparoscopic resection for exocrine carcinoma is comparable to the open approach with regard to oncologic outcomes and is a safe and effective oncologic procedure.

Essentially all published data regarding LDP for malignant lesions have been generated at high-volume institutions with significant experience in pancreatic resection surgery. Strasberg et al. [42] initially described the radical antegrade modular pancreatosplenectomy (RAMPS) procedure as an approach to distal pancreatectomy for cancer. That group has since demonstrated favorable outcomes for margins, node harvest, and long-term survival [41, 43]. The first report in the literature summarizing LDP for malignant lesions described a modified RAMPS procedure [38], and the RAMPS procedure has now been applied in both the laparoscopic setting and the robotic setting [44, 45]. Proceeding via a standardized approach may be beneficial should laparoscopic cancer resections become generalized.

Robotic Versus Laparoscopic Distal Pancreatectomy

The data in the previous sections suggest that LDP is equivalent if not superior to ODP in some respects. It has been suggested that the advantages of laparoscopy would be augmented by the application of robotic technology. As a minimally invasive approach, conventional laparoscopy suffers from its 2D surgical field, limited range of motion, fulcrum effect, and amplified instrument tremor [46, 47]. Robot-assisted surgery, by contrast, provides a stable 3D view with multiple degrees of freedom, improved dexterity, reduced operator fatigue, motion stabilization, and scale adjustment [47–50]. However, robotic surgery does have disadvantages. The size and positioning can be cumbersome and collisions between arms can prove troubling. For complex intra-abdominal surgery, the inability to change the position of the table is problematic. Lastly, and perhaps most importantly, robotic surgery is costly [51, 52]. Although the robot appears advantageous for the intricate dissection and reconstruction required in pancreatoduodenectomy, the advantage for left-sided resections is less obvious or convincing.

Robotic pancreatic resections were first reported nearly 10 years ago [19]. Since that time, a number of small series have chronicled the experience [18, 20, 53]. Inevitably, comparison between the conventional laparoscopic and robotic approaches ensued. Waters et al. [54] first compared ODP, LDP, and RDP in 2010. RDP was shown to be at the least equivalent, but the study suffered principally from small sample size ($N = 17$) and a lack of randomization among groups.

Two more recent studies have advanced the comparison of LDP and RDP. Kang et al. [55•] detailed their retrospective study of laparoscopic and robotic outcomes over approximately 4 years. The sample size remained small (45 cases in total, 20 LDP and 25 RDP). These investigators offered either LDP or RDP to their patients after informing them of the general characteristics of each approach. They noted no difference in demographics, length of resected pancreas, or tumor size, and thus selection bias appears to be minimized. Only two intraoperative qualities differed—mean operating time was significant higher in the robot group, and splenic preservation rate was also higher among these patients although the spleen-preserving rate for LDP became stable and approached that for RDP after approximately ten cases. There was no difference in transfusion, start of diet, complications, or length of stay. Notably, the total cost of RDP was almost twice that for the laparoscopic group.

Daouadi et al. [56••] have since provided the largest comparison of RDP and LDP to date. They performed 94 consecutive minimally invasive pancreatectomies laparoscopically from 2004 to 2007 prior to the availability of the robot at their institution. From 2008 to 2011, they performed 30 consecutive MIDP robotically. Because there was no overlap in the application of these approaches, selection bias again appears to be minimized. In this study, 44 % of lesions were malignant, indicating that complex tumors were being approached. The operating time in this study was significantly shorter for LDP than for RDP. However, although 16 % of LDP were converted to ODP, no conversions were reported in robotic cases. No differences were noted in morbidity, length of stay, readmission, complications, or pancreatic fistulae. Oncologic metrics appeared superior for RDP, as a higher proportion of resections were margin-negative (95 % for RDP vs 83 % for LDP) and the median number of lymph nodes harvested was greater (19 for RDP vs nine for LDP). There was no detailed cost analysis in this study nor was long-term survival assessed. Of note, most of the robotic resections were performed with two attending surgeons, indicating that they were resource-avid. That frequency was not provided for laparoscopic cases but is undoubtedly far lower. It could also be argued that techniques derived during the laparoscopic series are translatable to RDP; thus, the transition from LDP to RDP may have been smoother than that from ODP to LDP.

Data to this point indicate that robotic surgery is at the least a feasible strategy in distal pancreatectomy. Whether the technical advantages it provides can surmount the increased resource consumption remains to be seen. Principally, it is questionable whether the advances offered by

the robot are countered by experience with the laparoscopic approach, especially since the morbidity of the procedures is likely to be comparable.

Splenic Preservation in Laparoscopic Distal Pancreatectomy

Although distal pancreatectomy with concomitant splenectomy remains the procedure of choice for left-sided pancreatic malignant lesions, splenic preservation is attractive in the benign setting. The spleen does carry immunologic benefit and there is an increased risk of overwhelming sepsis following its removal [57–65]. Furthermore, concomitant splenectomy has been shown in some series to be a significant risk factor for complications, including pancreatic fistulae [66–68], although findings to the contrary have been published elsewhere [69]. As detailed already, numerous reports document higher rates of splenic preservation in LDP, and splenic salvage may yet be further facilitated with the robot. Although selection bias is certainly a factor, technical aspects are likely also involved. Given generally higher rates of splenic retention in MIDP, small series have begun to analyze the ideal technical approach.

Although several approaches have been described, splenic preservation in both MIDP and ODP has generally been accomplished in one of two ways. One is conservation of the splenic artery and vein with ligation of small branches to the pancreatic parenchyma. Alternatively, the Warshaw technique [65] features ligation of the splenic artery and vein proximally and distally with retention of the short gastric and left gastroepiploic vessels. In the laparoscopic setting, the latter approach has been reported to be faster and associated with less blood loss [38]. However, there are concerns regarding the long-term development of perigastric varices and spleen-associated morbidity with this approach [70, 71]. Although splenic vessel preservation seems favorable in this regard, recent evidence suggests a relatively high incidence of vascular obliteration following the splenic vessel preservation technique with resultant development of varices and splenic infarction [72].

Recently, outcomes following splenic-vessel-conserving and splenic-vessel-sacrificing MIDP have been compared. Butturini et al. [73•] performed a retrospective analysis of 43 patients who underwent laparoscopic spleen-preserving distal pancreatectomy—36 with splenic vessel conservation and nine with splenic vessel resection. No statistically significant difference was noted in overall complications, pancreatic fistulas, postpancreatectomy hemorrhage, reoperation, or length of stay. On 1-year follow-up imaging (computed tomography or magnetic resonance imaging), there was a trend toward increased perigastric/gastric varices after splenic vessel resection (60.0 vs 21.7 %) although this did not reach statistical significance because of the sample size. None of the patients with varices had a significant bleeding event, and very low incidences of bleeding despite development of such varices after splenic vessel resection have also been reported elsewhere [70, 71].

In the robotic setting, Hwang et al. [74•] published a series of 22 attempted spleen-preserving distal pancreatectomies. The rate of splenic salvage was 95 % (21/22). Seventeen cases featured splenic vessel conservation, whereas four required splenic vessel sacrifice. Operating time was noted to be longer in the splenic vessel sacrifice group, but in all cases it was intended to conserve the vessels from the outset. Thus, splenic vessel sacrifice occurred only by necessity, and it might be expected that these problematic cases were prolonged. Length of hospitalization and incidence of pancreatic fistula were not significantly different. Among patients in whom the splenic vessels were conserved, only 12.5 % developed partially or completely obliterated splenic veins at a median follow-up of 210 days. By contrast, all four patients who underwent splenic vessel sacrifice developed perigastric collateral vessels, and three of the four developed grade 1 submucosal gastric varices (also noted by computed tomography). Again no incidences of bleeding were reported.

Whether splenic vessel preservation or sacrifice is superior remains uncertain. In terms of long-term effects, prospective studies comparing the two approaches are lacking, and preoperatively evaluable patient characteristics favoring one approach over the other are not well understood. Notably, splenic vessel sacrifice may be associated with a higher rate of splenic infarction in one subgroup—elderly individuals. Baldwin et al. [75] reported that splenic vessel division resulted in splenic infarcts in 100 % of patients more than 70 years old, 75 % of whom required splenectomy for management. This has not been confirmed elsewhere and was derived from a very small sample size ($N = 4$).

Importantly, studies comparing splenic preservation by these two approaches have often failed to contrast the techniques on an intent-to-treat basis. Patients for whom splenic preservation was achieved with vessel resection were commonly approached with the intent to preserve the vessels initially; splenic vessel division occurred only because of technical issues such as bleeding. One recent study has detailed an approach that has some promise for reliable vessel preservation. Nakamura et al. [76] described their approach to splenic-vessel-preserving LDP which features separation of the pancreas from the retroperitoneum laterally first. Their rationale is that the splenic vessels are more easily separated from the parenchyma in this manner, thus facilitating a safer retrograde dissection. The splenic artery was also temporarily occluded when

dividing its branches to the pancreatic parenchyma to minimize bleeding. In their retrospective study, only six of 14 distal pancreatectomies were completed with vessel preservation in the years prior to the institution of this lateral approach. Since 2009, all eight of their distal pancreatectomies have been completed with vessel preservation, all performed via the lateral approach. Although this is interesting, enthusiasm for it must be tempered by the limited sample size.

Conclusions

The widespread application of minimally invasive approaches represents arguably the greatest advance in general surgery over the past quarter century. Greater familiarity with the tools and techniques of laparoscopy has gradually led to its use in increasingly complex procedures. Because of its retroperitoneal location and proximity to major vasculature, the pancreas has thus far been the last frontier in abdominal surgery. However, MIDP has steadily gained favor and continues to gain momentum with realization of acceptable results for malignant lesions.

This review has focused on recent advances in the literature regarding MIDP. Detailed comparisons have been made between ODP and LDP that suggest the latter approach has several potential advantages: less blood loss, greater splenic preservation rates, fewer overall complications, and shorter durations of hospital stay. LDP in the setting of malignant lesions has now been shown to be feasible and to this point has no documented disadvantages versus the open approach. Although several of the purported advantages of LDP have yet to be clearly evidenced, technical strides continue to be made. RDP is now being performed successfully with results that appear equivalent to those of LDP and ODP, but cost-effectiveness remains in question. Splenic preservation in MIDP has been achieved through multiple approaches, with no clear consensus on which is superior. Additionally, two institutions have now published their single-center experience with single-incision LDP [77, 78]. Although such techniques may not produce advantages over conventional LDP, they illustrate the advancing application of minimally invasive approaches in pancreatic surgery. Continued refinements in technique may provide heretofore unrealized advantages to the patient.

Clearly the findings that have been documented in the MIDP literature need to be validated in multicenter, randomized fashion. Whether these reported outcomes persist when use of MIDP disperses to pancreatic surgeons who do not currently employ it also remains to be seen. Although some have argued that the laparoscopic approach represents a new standard in left-sided resections, there are undoubtedly selection biases in many of the retrospective studies that predispose ODP groups to higher rates of morbidity. However, a recent report from a high-volume institution suggests that more arduous cases in increasingly complicated cases are being approached in minimally invasive fashion [79]. Thus, it appears as though the learning curve of laparoscopic pancreatic surgery is leveling to a point where comparative, randomized studies are feasible. With more experience, technical advances in the realm of minimally invasive pancreatectomy are very likely to continue. However, perhaps more importantly, scientifically rigorous comparisons of the cost and efficacy of MIDP versus ODP in complex pancreatic lesions are now on the verge of being made. Stay tuned.

Disclosure Major K. Lee IV and Charles M. Vollmer declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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