Minimally invasive versus open distal pancreatectomy for ductal adenocarcinoma (DIPLOMA)—a difficult question to answer

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Since the introduction of laparoscopy as an adjunct to abdominal surgery in the 1980's, surgeons have sought to compare the clinical outcomes of minimally invasive procedures with their parent operations. Initial reports of technical feasibility (1,2) are classically followed by evaluations of safety and efficacy (3,4) and if applicable, oncologic outcomes (5,6). In their recently study, *Minimally Invasive versus Open Distal Pancreatectomy for Ductal Adenocarcinoma (DIPLOMA)* (7), van Hilst *et al.* attempt to compare technical and oncologic outcomes between these increasingly common pancreatic resections.

Open distal pancreatectomy (ODP) was originally described over 100 years ago and rarely performed, most often in the face of otherwise unsurvivable malignancy, due to the procedure's associated morbidity and mortality (8). As pancreatic surgery entered the modern era in the late 1990's, reports from high-volume centers described vastly improved safety and efficacy (9,10). renewing interest in the procedure for a wider array of patients. Ongoing technical refinements to the open approach were made into the early 2000's (11) demonstrating continued interest in methodologies to maximize the procedure's oncologic benefit. During this same period, laparoscopic distal pancreatectomy (MIDP) made its debut (12). Since that time multiple systematic reviews and cohort studies have indicated safety and efficacy with the minimally invasive approach (13-15). However, due to the relatively low incidence of the procedure globally, high quality randomized-controlled data are lacking.

On behalf of the European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS), van Hilst *et al.* aimed to address this lack of data by performing a large multi-institutional retrospective cohort study, evaluating over 1,200 patients for their analysis. Thirty-four institutions, primarily in Europe, each performed a median of 30 distal pancreatectomies per year, 14 for pancreatic ductal adenocarcinoma (PDAC). In an attempt to widen generalizability, the authors allowed broad histopathological inclusion criteria for patients with distal PDAC including mucinous non-cystic carcinomas, signet ring cell carcinomas, adenosquamous carcinomas, and undifferentiated/mixed-type carcinomas of the pancreas. However, the authors prudently excluded patients with celiac trunk involvement, those who had previously undergone pancreaticoduodenectomy, and those only became resectable after undergoing neoadjuvant chemotherapy.

Preoperative patient characteristics after propensity score matching were equivalent between ODP and MIDP, indicating relative intergroup homogeneity. Ninety-six percent of MIDPs were able to be matched with a corresponding ODP. Intraoperative blood loss was lower in the MIDP group, a finding consistent with other studies comparing laparoscopic and open approaches for intraabdominal resections (5,16) and is likely due to improved visualization with laparoscopic magnification as well as the hemostatic effects of pneumoperitoneum. Serious postoperative morbidity and incidences of a pancreatic fistula were also equivalent in this study, supporting the findings of a recent Cochrane database review on this topic (17). The authors also demonstrated

comparable overall survival (OS) between MIDP and ODP. The reported median OS of 28 months is consistent with other recent investigations evaluating modern adjuvant chemotherapeutic regimens (18), however this finding is somewhat surprising as similar patients with body/tail lesions have previously been shown to have a poorer prognosis (19).

The authors do focus on several key findings in their data including differences in margin status, lymph node retrieval, and Gerota's fascia resection. The R0 resection rate was significantly higher with MIDP when compared with ODP (67% *vs.* 58%, P=0.019), a finding at odds with three previous studies comparing these techniques (20-22). van Hilst and colleagues appropriately pointed out that margin status is a notoriously problematic outcome to measure, as the specifics of pathologic assessment and actual definitions of R0/R1 can differ significantly between studies. While this may be true, the authors failed to describe why ODP should be inferior to MIDP in this regard. As this was not a randomized study, it is not unreasonable to expect that patients selected for OPD may have had tumors placing them at lower chance for an R0 resection. While propensity matching did adjust for tumor size, tumor location (body/tail), and involvement of other organs, more subtle morphologic differences on preoperative imaging that may have affected treatment allocation were not controlled for and may have affected this result.

Lymph node retrieval was noted to be inferior in the MIDP group, as the median number of lymph nodes retrieved was nearly 60% higher (22 *vs.* 14, P<0.001) in patients who underwent an open operation. While this finding is statistically significant, the clinical significance is less clear. Recent reports have demonstrated that obtaining at least 10 or 11 lymph nodes in pancreatectomy specimens for PDAC is sufficient (23,24), with both groups in the DIPLOMA study meeting this benchmark. There are no recent data to suggest obtaining additional lymph nodes beyond this standard confers a prognostic or survival advantage. In fact, the lymph node ratio (LNR) has been reported as the strongest prognostic factor after resection for pancreas cancer (25). In this study both ODP and MIDP showed comparable LNR (0.06 *vs.* 0.08, P=0.403) corresponding with the equivalent observed OS. Rates of resection of Gerota's fascia are also reported, with ODP noted as superior to MIDP (60% *vs.* 31%, P<0.001). The authors suggest that removal of Gerota's fascia may be important in achieving an R0 resection, particularly in reference to the specimen's tangential margin. If this

holds true, the study's finding of a lower R0 resection rate in the ODP group may be related to the higher rates of lymphovascular and perineural invasion observed in these patients. Moreover, a recent meta-analysis including six studies comparing radical antegrade modular pancreatosplenectomy (which includes Gerota's fascia) versus standard distal pancreatectomy showed no difference in recurrence rates, disease-free survival, or OS (26).

DIPLOMA is a well-performed study addressing a clinical question complicated by low disease incidence, heterogeneous biology, and subtle technical elements which make comparing ODP and MIDP exceedingly difficult. Despite its large size and multi-institutional nature, it is still at its core a retrospective cohort study. However, in utilizing propensity matching, the authors make a good-faith effort to reduce the impact of treatment allocation bias which is the most common pitfall in studies comparing open and minimally invasive approaches. MIDP most likely confers the same short-term clinical benefits (decreased pain, decreased length of stay, etc.) demonstrated across a multitude of other minimally invasive abdominal procedures. However, the oncologic benefits—or liabilities—of the approach have not been demonstrated with an acceptable level of certainty; an issue the authors suggest could be addressed with a randomized trial. Given the relatively high recurrence rates and low OS in patients with PDAC, demonstrating oncologic superiority between MIDP and ODP may be impossible, until modern systemic therapies enable these patients to live longer and facilitate distinction between these two surgical approaches.

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Footnote

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