Minimally invasive surgery for pancreatic cancer—are we there yet?—a narrative review

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Objective: The aim of this review article is to evaluate the current status of minimally invasive pancreatic resections (MIPR) for pancreatic ductal adenocarcinoma (PDAC), in light of the present evidence.

Background: Published data, largely in the form of retrospective studies and a few prospective/randomized controlled trials have confirmed feasibility, safety, and equivalent short-term outcomes of MIPR in experienced hands. Hence, several recent evidence-based international consensus guidelines have stated MIPR to be at par with the open approach, when these surgeries are performed at high-volume centers. However, longer operative duration, high conversion rates, inferior oncological outcomes, and increased mortality reported in low-volume centers, especially during minimally invasive pancreaticoduodenectomy remains a matter of concern, questioning its broad applicability. Hence, distal pancreatic resections are adopted more widely with a minimally invasive approach as compared to pancreatic head resections. Also, MIPR for PDAC in particular, remains controversial due to lack of high quality data evaluating long-term outcomes of MIPR for PDAC alone. Considering the ongoing impact of neoadjuvant treatment on pancreatic cancer surgery and the corresponding increase in vascular resections and arterial divestment procedures, applicability of MIPR in this setting remains questionable.

Methods: Medline, PubMed, Embase, Cochrane Library, and various international evidence-based guidelines were searched for the current status of minimally invasive resections for pancreatic cancer (PDAC).

Conclusions: The available evidence establishes the feasibility and safety of MIPR, however for PDAC the widespread application remains controversial owing to a dearth of literature evaluating the long-term outcomes. Apart from the outcomes, establishing the exact indications, appropriate patient selection, enhanced cost, and learning curve issues need further studies.

Keywords: Minimally invasive pancreatic resections (MIPR); laparoscopic pancreaticoduodenectomy (LPD); robotic pancreaticoduodenectomy (RPD); laparoscopic distal pancreatectomy (LDP); robotic distal pancreatectomy (RDP)

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Introduction

Minimally invasive surgery (MIS) has gradually evolved, especially in the past two decades; and now is an integral part of management for almost all digestive diseases. In gastrointestinal (GI) cancers, MIS has shown equivalent results to the open approach for early gastric and colorectal cancers (1-3). Technological advances and the development of specific skill sets required for this approach by dedicated surgical teams led to rapid development in laparoscopic and robotic surgery for GI cancers.

The minimally invasive approach did not gain much popularity for pancreatic surgery for a long time since its first introduction in the early 1990s (4,5). Probable reasons being the anatomic disadvantages, i.e., retroperitoneal location of the organ, its intimate relations with major blood vessels and, the soft, friable, unforgiving nature of the gland. However, much progress has been made in the past decade and today MIS is widely accepted for managing benign pancreatic lesions or tumors with low malignant potential, especially in the distal pancreas.

MIPR has the potential to provide unreplaceable advantages to patients undergoing surgery for pancreatic cancer in terms of early recovery, fewer complications, reduced hospital stay, and cosmetically pleasing wounds. Several retrospective studies and a few randomized trials have demonstrated the safety and feasibility of minimally invasive pancreatic resections (MIPR), i.e., minimally invasive pancreaticoduodenectomy (MIPD), and minimally invasive distal pancreatectomy (MIDP). Although these studies reported favorable outcomes of certain parameters with MIS (lower blood loss, morbidity, and shorter hospital stay); the longer operative duration, high conversion rates, inferior oncological outcomes, and increased mortality reported in low-volume centers remain a matter of concern. Hospital volumes have a strong impact on postoperative outcomes for major pancreatic resections, even with the conventional open approach (6). With MIPR, the surgical complexity increases further, and hence it is recommended that such procedures are performed at specialized centers with a high volume of pancreatic surgery. Furthermore, the mid-term and long-term outcomes of MIPR for pancreatic ductal adenocarcinoma (PDAC) along with the issues of the indications and learning curve are controversial and need further assessment.

Also, as neoadjuvant therapy (NAT) is being more utilized for resectable and borderline resectable pancreatic ductal adenocarcinoma (PDAC), prospective evaluation of MIPR for PDAC after NAT remains the job at the fore.

In the present article, we intend to provide an overview of the progress made so far and the current position of MIPR for PDAC. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-131/rc).

Methodology

Medline, PubMed, Embase, Cochrane Library, and various international evidence-based guidelines (like Miami International Evidence-based Guidelines, International & Japanese Hepatopancreaticobiliary Association Guidelines) were searched for the current status of minimally invasive resections for pancreatic cancer/PDAC. Databases were searched using combinations of pancreatic cancer and the role of minimally invasive pancreatic resections based on both MeSH headings and text words. MeSH terms used included but were not limited to, 'pancreatic neoplasms', 'pancreatic cancer treatment', 'minimally invasive pancreatic resections', 'minimally invasive pancreaticoduodenectomy', 'minimally invasive distal pancreatectomy', 'laparoscopic distal pancreatectomy', 'robotic pancreaticoduodenectomy', 'robotic pancreatico splenectomy and 'early post-operative outcomes', 'oncological outcomes', 'long-term outcomes', 'cost-effectiveness' and 'cost-benefit. Studies published in English as peer-reviewed journal articles between January 1994 and September 2021 were considered eligible for inclusion in this review.

Discussion

Minimally invasive distal pancreatectomy (MIDP)

Left pancreatic resections are adopted more commonly for MIPR owing to a less complex and arduous nature of the surgery, requiring resection alone without any need for reconstruction, as compared to the right-sided resections i.e., pancreaticoduodenectomy (PD).

The standard surgery for resectable pancreatic body/tail adenocarcinoma requires a RAMPS (Radical Antegrade Modular Pancreatico-splenectomy) procedure. With a medial to lateral approach, this technique allows greater ability to obtain R0 resection modulating the posterior or retroperitoneal dissection plane (7,8). Also, there is some evidence to suggest that the routine excision of the upper half of Gerota's fascia for these tumors provide additional oncological benefit (9).

The majority of the current evidence for MIDP is from single-center retrospective studies with surgeries performed for mixed pathologies including benign and malignant lesions. Comparable outcome measures such as operative time, postoperative morbidity, and mortality have been reported in most of these studies comparing MIDP with open distal pancreatectomy (ODP). But in addition, MIDP offered less blood loss and a shorter hospital stay although the operative time can be significantly longer for MIDP as per one of the randomized controlled trials (RCT) (10). However, as the minimally invasive approach becomes more and more common and when surgeons negotiate the learning curve, the operative time is likely to reduce. As regards the short-term oncological outcomes, the general trends have shown equivalent results for MIDP and ODP.

Laparoscopic distal pancreatectomy (LDP)

The first LDP was performed and reported by Cuschieri in 1994 (11). At present, just more than 25 years later after the first description of LDP, two RCTs have been completed together with several retrospective studies and meta-analysis of these studies evaluating LDP.

The first published RCT by de Rooij *et al.*, LEOPARD-1 trial, was a multicenter study with 108 patients (6). Operative procedures were performed by surgeons from medium- and high-volume hospitals after going through a structured training program. Patients with pancreatic body/tail tumors (benign and malignant) without any vascular involvement, were randomized to MIDP (laparoscopic or robotic) and ODP in a 1:1 ratio, and the patients were blinded by using large abdominal bandages. The primary outcome was functional recovery time which included factors namely patient mobility, pain control, oral intake, need for intravenous fluids, and surgical site infections. The MIDP group had less intraoperative blood loss (150 *vs.* 400 mL; P<0.001), however; the operative time was longer (217 *vs.* 179 min; P=0.005). Conversion to open was observed in 8% of cases in MIDP. The perioperative morbidity, grade B/C pancreatic fistula rate, and 90-day mortality was comparable in both groups. The functional recovery time was 4 days (range, 3–6 days) after MIDP as against 6 days (range, 5–8 days) after ODP (P<0.001). Each parameter for functional recovery was reached faster with MIDP with a shorter hospital stay. The short-term quality of life was better with MIDP, while the overall cost of treatment was comparable to ODP. Although the short-term oncological outcomes i.e., the R0 resection and lymph node yield was comparable, only 23 (21%) patients had PDAC histology.

The other RCT, LAPOP, was a single-center trial with a superiority design and included 58 patients comparing LDP and ODP (12). The inclusion criteria and randomization were similar to the LEOPARD1 trial with the primary endpoint being the length of hospital stay. Blood loss was less with LDP (50 *vs.* 100 mL; P=0.018), and the operative time was similar to ODP. One patient was converted to open (3.4%) in the LDP group. Perioperative morbidity and mortality were comparable. The median hospital stay was 5 days (range, 4–5 days) after LDP *vs.* 6 days (range, 5–7 days) in the ODP group (P=0.002). Again, this study also suffered for comparison of short-term oncological outcomes as only 8 (13.7%) of the included patients were PDAC.

An individual patient data meta-analysis, combining data from both LEPORD1 and LAPOP trials (n=166) compared outcomes after MIDP and ODP (13). The primary endpoint was the rate of major (Clavien-Dindo > III) complications within 90 days in the post-operative period and was comparable after MIDP and ODP (21% *vs.* 35%, P=0.148).

Multiple other retrospective studies and meta-analyses have consistently reported benefits in terms of less operative blood loss and shorter hospital stay with LDP, together with comparable complication rates and mortality. In general, the short- and long-term oncological outcomes are also reported to be similar although with a smaller number of patients with PDAC (*Table 1*).

Robotic distal pancreatectomy (RDP)

The robotic platform is well-suited for complex abdominal surgeries due to its inherent advantages in the form of enhanced visualization, improved instrument dexterity, and surgeon ergonomics. It is being increasingly utilized for distal pancreatic resections since its first description by Melvin in 2003 (1), however is still less commonly used as compared to LDP (30). In general, studies addressing surgery specifically in malignant tumors have revealed no advantage of RDP over LDP with an equivalent rate of R0 resection, lymph node retrieval, and duration to adjuvant treatment. In studies comparing open DP, LDP, and RDP; RDP was associated with lower blood loss and lower clinically significant postoperative complications, although with a longer operative time and a higher cost (31-33).

In a systematic review by Zhao *et al.*, RDP was associated with less blood transfusion, fewer lymph nodes harvested, lower complications and shorter hospital stay as compared to ODP (34). The rate of spleen preservation, positive

Table 1 Oncological and perioperative outcomes of minimally invasive vs. open distal pancreatectomy for pancreatic cancer

Authors/year	Procedure/numbers	Propensity matching	Oncological outcomes								Per-operative outcomes							
			R0 resection (%)	P value	LN Harvest	P value	Overall survival (months)	P value	Adjuvant chemotherapy (%)	P value	Operative time (min)	P value	Blood loss (mL)	P value	Hospital stay (days)	P value	Post-operative complication	P value
Kooby *et al.* 2010 (14)	Lap/Open; 23/189	–	74/73	NS	13.8±8.4; 12.5±8.5	NS	MST 11 months; 11 months	NS	57; 70	NS	238.4±68.1; 230.4±80.4	NS	422±473; 790±828	0.004	7.4±3.4; 10.7±6.3	0.03	–	–
Magge *et al.* 2013 (15)	MIS (Lap &Robotic)/Open; 28/34	–	86/88	NS	11 (IQR: 8–20); 12 (IQR: 6–19)	NS	Only comparison provided	NS	–	–	317±23; 294±24	NS	790±828; 290±60	0.006	6 (IQR: 3); 8 (IQR: 2.75)	0.03	39% *vs.* 50%	NS
Hu *et al.* 2014 (16)	Lap/Open; 11/23	–	100/100	NS	14.8±4.5; 16.1±5.7	NS	42.0±8.6 months; 54.0±5.8 months	>0.05	–	–	150.0±54.0; 160±48.0	NS	100 [50–400]; 150 [50–350]	NS	5.2±2.5; 8.6±3.9	0.01	–	–
Rehman *et al.* 2014 (17)	Lap/Open;8/14	–	88/86	NS	16 [1–27]; 14 [0–26]	NS	MST; 33 *vs.* 52 months	NS	–	–	376 [300–534]; 274 [180–420]	0.009	306 [250–535]; 650 [145–1,300]	NS	8 [5–14]; 12 [6–21]	0.05	37% *vs.* 42%	NS
Lee *et al.* 2014 (18)	MIS (Lap &Robotic)/Open; 10/40	Yes	100/87.5	NS	11.7±7.2; 12.1±8.1	NS	Only comparison provided	0.05	70; 65	NS	330±168.2; 253.3±124.7	NS	440±382.1; 625.4±878.8	NS	12.7±7.1; 22.1±27.1	0.05	20% *vs.* 32.5%	NS
Shin *et al.* 2015 (19)	Lap/Open; 70/80	–	75.7/83.8	NS	12 [1–34]; 10 [1–64]	NS	MST; 33 *vs.* 29 months	NS	78.6; 68.8	NS	239 [125–397]; 254 [115–573]	NS	–	–	9 [5–29]; 12 [7–87]	<0.001	20% *vs.* 25.7%	NS
Sulpice *et al.* 2015 (20)	Lap/Open; 347/2406	–	–	–	–	–	MST; 62.5 *vs.* 36.7 months	0.0001	–	–	–	–	–	–	14.9±8.9; 19.6±14.6	<0.0001	6.6% *vs.* 10.4%	NS
Sharp *et al.* 2015 (21)	Lap/Open; 144/625	–	87/78	0.04	14.9±10.0; 13.3±9.9	NS	–	–	–	–	–	–	–	–	6.8±4.6; 8.9±7.5	<0.001	–	–
Zhang *et al.* 2015 (22)	Lap/Open; 17/34	–	94/85	NS	9 [5–15]; 8 [2–22]	NS	MST; 14 *vs.* 14 months	NS	76.5; 76.5	NS	190 [100–390]; 245 [155–420]	NS	50 [30–500]; 400 [100–3,900]	0.000	13 [4–23]; 15.5 [6–40]	0.022	35.2% *vs.* 41%	NS
Stauffer *et al.* 2016 (23)	Lap/Open; 44/28	–	95/82	NS	25.9 [5–48]; 12.7 [1–45]	0.0001	MST; 26.6 *vs.* 26.4 months	NS	75.6; 75	NS	254 [99–521]; 266 [131–543]	NS	332 [10–2,650]; 874 [150–3,400]	0.00012	5.1 [2–17]; 9.4 [4–36]	0.0001	13.6% *vs.* 25%	NS
Anderson *et al.* 2017 (24)	MIS (Lap &Robotic)/ Open; 505/1302	–	85/79	<0.001	12 [7–19]; 12 [7–19]	NS	3 yr OS 55%; 3 yr OS 52%	NS	57.8; 53.8	NS	–	–	–	–	6 [5–8]; 7 [6–10]	0.0001	–	–
Plotkin *et al.* 2017 (25)	MIS (Lap &Robotic)/Open; 166/335	–	–	–	–	–	–	–	–	–	239±9.0; 250±6.2	NS	–	–	5±0.31; 7±0.51	0.009	31% *vs.* 42%	NS
Kantor *et al.* 2017 (26)	Lap/Open; 349/1,205	–	82/75	<0.001	14.0±11.7; 14.8±12.0	NS	MST; 29.9 *vs.* 24 months	NS	67.9; 61.8	NS	–	–	–	–	7.1±6.0; 8.7±7.3	<0.01	–	–
Bauman *et al.* 2017 (27)	Lap/Open; 33/46	–	77/87	NS	14.5±1.1; 17.5±1.2	NS	MST; 17.9 *vs.* 15.1 months	NS	61; 63	NS	3.9±0.2 (h); 4.2±0.2 (h)	NS	310±68; 597±95	0.016	7.6±1.4; 9±0.7	0.44	52% *vs.* 70%	NS
Raoof *et al.* 2018 (28)	Lap/Open; 563/563	Yes	85/81	NS	12 [7–18]; 1 [6–18.5]	NS	3 yr OS 41.6%; 3 yr OS 36.0%	NS	–	–	–	–	–	–	6 [5–8]; 7 [5–9]	<0.001	–	–
van Hilst *et al.* 2019 (29)	MIS (Lap &Robotic)/Open; 340/340	Yes	67/58	0.01	14 [8–22]; 22 [14–31]	<0.001	MST; 28 *vs.* 31 months	NS	76; 73	NS	240 [180–295]; 230 [178–286]	NS	200 [60–400]; 300 [150–500]	0.001	8 [6–12]; 9 [7–14]	<0.001	18% *vs.* 21%	NS

MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy; LDP, laparoscopic distal pancreatectomy; RDP, robot-assisted distal pancreatectomy; MIPD, minimally invasive pancreatoduodenectomy; OPD, open pancreatoduodenectomy; LPD, laparoscopic pancreatoduodenectomy; RPD, robot-assisted pancreatoduodenectomy.

margin, pancreatic fistula, and mortality were comparable. Another systematic review and meta-analysis by Niu *et al.* observed longer operative time, shorter hospital length of stay, and a higher rate of spleen preservation with RDP, in comparison with LDP (35). Also, hospital stay and overall complications were lower with RDP compared to ODP.

Data on long-term oncological outcomes for PDAC after RDP are limited. In a recent retrospective study from a national cohort, Nassour *et al.* compared oncological outcomes between RDP and ODP for PDAC alone (36). Lymph node retrieval, as well as overall survival (33.3 *vs.* 24.9 months, P=0.001), was better with RDP. The perioperative mortality was also lower in the RDP group. However, the authors acknowledged a potential for surgeon bias in selecting smaller tumors with no vascular or concomitant organ involvement for minimally invasive surgery while reserving challenging cases at risk of postoperative complications for the open approach, which could have been reflected in the analysis.

Learning curve (LC)

Regarding the LC analysis for MIDP, the evidence is heterogeneous. The Dutch Pancreatic Cancer Group has shown a seven-fold increase in LDP with a decrease in conversion rates and hospital stay via implementation of the Longitudinal Assessment and Realization of Laparoscopic Pancreatic Surgery program (LAELAPS)-1 (37). This highlights that standardization of the technique for MIPR may contribute to the optimal surgeon and patient outcomes. In studies where operative time and estimated blood loss were used to assess the LC, 10–20 cases have been proposed to reach proficiency (38). In a recent systematic review, LC for LDP was comparable to RDP. MIPD had significantly longer LC as compared to RDP and LDP. The study also highlighted the impact of institutional LC being smaller as compared to individual surgeon LC (39).

For optimizing the perioperative outcomes depending on the surgeon's or institution's LC phase, appropriate case selection remains extremely important. For this purpose, scoring systems have been proposed to anticipate challenges during the intra- and post-operative periods for MIDP. The original Difficulty Scoring System (DSS) for LDP by Osaka *et al.*, later modified by Italian study includes the following parameters to grade difficulty based on the type of operation, presence of malignancy, neoadjuvant treatment, the proximity of the pancreatic transection line to the portal vein, tumor proximity to major vessels, tumor extension to peripancreatic tissues, left-sided portal hypertension and splenomegaly (40). Using these parameters, LDP was graded into low, intermediate, and high difficulty levels. Operative time, blood loss, and the conversion rate were considered as surrogate markers of difficulty. The DSS may allow for surgical stratification, better patient counseling, and graded surgical teaching while implementing a structured MIDP program (41).

Oncological outcomes (*Table 1*)

Thus far, no RCT has evaluated equivalence or superiority of MIDP with open surgery for pancreatic ductal adenocarcinoma (PDAC). The radicalness of surgery requires a completely different approach and training for performing MIDP in PDAC, i.e., RAMPS procedure as compared to that for benign or low-grade malignant tumors. The clearance of entire lymph node stations including 14a, 16a1 & 16a2, dissecting along the left border of SMA and celiac axis is an established standard of care for DP for PDAC, also possibly with excision of the upper part of Gerota's fascia. Although technically this clearance is possible with MIDP, a dedicated approach by high-volume centers is required for consistent implementation of this procedure.

A large pan-European retrospective study (DIPLOMA) provides important data comparing MIDP and ODP including patients with PDAC alone (29). The primary aim of this study was to compare oncological outcomes. Consecutive patients undergoing distal pancreatic resection among 34 participating centers with laparoscopic, robotic, or open approaches were analyzed. In the total cohort of 1,212 cases, after propensity matching, 340 MIDPs were compared to 340 ODPs. The majority of MIDPs were LDPs, with only 16 patients undergoing robotic distal pancreatectomy (RDP). A higher conversion rate of 19% was observed with MIDP, probably related to the difference in the learning curve in the participating centers. Short-term clinical advantages of MIDP were observed in the comparison. The median intraoperative blood loss was less with MIDP (200 *vs.* 300 mL, P=0.001) and the median hospital stay was also shorter (8 *vs.* 9 days, P=0.001). R0 resection rate was higher with MIDP (67%) as compared to OPD (58%, P=0.019), however; the OPD group had a significantly higher number of patients with node-positive disease, lymphovascular emboli, and peri-neural invasion. The lymph node retrieval was significantly less in the MIDP group (14 *vs.* 22, P<0.001), as well as in patients with the adrenal gland and Gerota's fascia resection. Although the overall median survival was comparable in both groups

Table 2 Ongoing randomized controlled trials evaluating minimally invasive pancreatic resection, MIPR

Trial/region/design	Sample size	Results expected	Arms	Primary outcome measure
DIPLOMA (NCT04483726), International, Multicentre Patient- and assessor blinded	258	2021	MIDP (RDP or LDP) *vs.* ODP	R0 resection
(NCT03957135), Korean, Multicentre Non-blinded	244	2025	LDP *vs.* ODP	2-year survival
(NCT03792932), Chinese, Multicentre Non-blinded	306	2024	LDP *vs.* ODP	2-year disease free survival
PORTAL (NCT04400357), China, Phase III Multicentre Patient blinded	244	2024	RPD *vs.* OPD	Time to functional recovery
(NCT04171440), USA, Phase III Single-centre Patient-blinded	240	2025	MIPD (RPD or LPD) *vs.* OPD	Time to functional recovery

MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy; LDP, laparoscopic distal pancreatectomy; RDP, robot-assisted distal pancreatectomy; MIPD, minimally invasive pancreatoduodenectomy; OPD, open pancreatoduodenectomy; LPD, laparoscopic pancreatoduodenectomy; RPD, robot-assisted pancreatoduodenectomy.

(29 months in MIDP and 31 months in ODP), with the opposing differences in R0 resection rate, resection of Gerota's fascia, and lymph node retrieval, the authors concluded that the oncological safety of MIDP remains uncertain.

A systematic review comparing MIDP with ODP for PDAC showed a significant heterogeneity indicating treatment allocation bias towards MIDP. Patients undergoing MIDP had smaller tumors with less perineural and lymphovascular invasion (42). *Table 1* highlights the oncological and perioperative outcomes of minimally invasive distal pancreatectomy and open distal pancreatectomy for pancreatic cancer. Hence, the long-term oncological outcomes with this procedure, purely for left-sided PDAC, need to be evaluated before wide adoption of MIDP for PDAC (14-28).

In this background, the following three important ongoing RCTs would provide valuable information as regards the real oncological safety of MIDP for PDAC (*Table 2*).

The DIPLOMA multicenter trial is recruiting 258 PDAC patients from 11 countries undergoing MIDP (LDP/RDP) and ODP, with the primary endpoint being R0 resection status (microscopic margins), and secondary endpoint of overall survival.

A multicentric Korean RCT with a non-inferiority design plans to include 244 resectable body/tail PDAC patients. LDP and ODP will be compared with a primary endpoint of 2-year survival.

Another RCT from China is also comparing LDP and OPD for patients with pancreatic body/tail malignant tumors and will include 306 patients with a primary endpoint of 2-year disease-free survival.

Minimally invasive pancreaticoduodenectomy (MIPD)

MIPD remains a highly complex and demanding procedure, as the resection involves more meticulous and difficult dissection along the superior mesenteric artery (SMA) and portal vein (PV) followed by an extremely challenging reconstruction procedure, specially pancreaticojejunostomy (PJ). The challenge of achieving R0 resection is even more for PDAC, as compared to other malignancies in the periampullary region. R0 resection rate for pancreatic head cancers has been traditionally reported to be lower (43). In this context, SMA first approaches have become a standard routine for all open PD's (OPD) for pancreatic head cancers (44,45). The different artery first approaches can be utilized during MIPD, however, requires significant training with a long LC.

The majority of the current evidence for MIPD is from single-center retrospective studies, systematic reviews, and meta-analyses with only four published RCTs.

Laparoscopic pancreaticoduodenectomy (LPD)

At present, the evidence is conflicting as regards the safety and reproducibility of LPD. The majority of retrospective studies and three of the published RCTs have reported equivalent short-term outcomes with LPD as compared to the OPD.

The first published RCT, PLOT (Randomized

Clinical Trial of Laparoscopic Versus Open Pancreaticoduodenectomy for Periampullary Tumors); was a single-center, non-blinded RCT from India. The trial included 64 patients with periampullary tumors, randomized in a 1:1 ratio to LPD or OPD, with the primary outcome variable being the length of hospital stay. LPD was associated with longer operative time but reduced intraoperative blood loss. Hospital stay was shorter with LPD (7 *vs.* 13 days; P=0.001) as compared with OPD. Short-term perioperative outcomes, including major morbidity, mortality, rates of postoperative pancreatic fistula, delayed gastric emptying, postoperative hemorrhage was comparable. Also, parity was observed in the short-term oncological outcomes, i.e., lymph node yield, and R0 resection, between both groups (46).

The second single-center RCT, PADULAP (Comparison of Perioperative Outcomes Between Laparoscopic and Open Approach for Pancreaticoduodenectomy) from Spain, included 66 patients with benign, premalignant, or malignant pancreatic tumors with a 1:1 randomization to LPD and OPD. The primary endpoint of this trial too was the length of hospital stay. Like the PLOT trial, longer operative time and shorter hospital stay were observed in the LPD arm (13.5 *vs.* 17 days; P=0.024). Fewer Clavien-Dindo grade III or higher complications were reported in the LPD Group, however; pancreas-specific complications were comparable between both groups. The lymph node yield and R0 resection rates were similar (47).

The third RCT, LEOPARD-2 (Laparoscopic Versus Open Pancreaticoduodenectomy for Pancreatic or Periampullary Tumours), evaluates LPD versus OPD, was a large scale multicenter, patient-blinded RCT (phase II/III). The included four centers performed 20 or more PDs annually and 20 LPDs before trial participation. The estimated sample size was 136 patients. The primary outcome of the phase II study was safety i.e., perioperative complications and mortality, and that for the phase III study was time to functional recovery. The study was prematurely terminated by the data and safety monitoring board because of a difference in 90-day complication-related mortality. The mortality in the LPD group was 10% (n=5/50) as compared to 2% (n=1/49) in the OPD group. Causes of mortality included bowel ischemia from intraoperative vascular damage, post-pancreatectomy haemorrhage, and POPF. The authors concluded that these safety concerns were unexpected and worrisome, especially in the setting of trained surgeons working in centers performing 20 or more PDs annually. Experience, learning curve, and annual volume might have influenced the outcomes; and future research should focus on these issues (48).

The fourth and the most recent multicenter, open-label RCT by the MITG-P-CPAM group from China is the largest trial published to date. Eligible patients (n=656) were randomly assigned (1:1) to undergo either LPD (n=328) or OPD (n=328). PD was performed for benign, premalignant, or malignant indications. The data collectors, outcome assessors, and data analysts were blinded regarding the study arm, whereas patients and surgeons were unblinded. LPD and OPD were performed by experienced surgeons who had already done at least 104 LPD procedures individually. The primary endpoint was the length of hospital stay. All analyses were performed on a modified intention-to-treat basis. After excluding patients with major deviations while including those with crossover (between the LPD and OPD arms), 297 patients in each arm were compared. The postoperative length of stay was significantly shorter for patients in the LPD group (median 15 *vs.* 16 days; P=0.02) and 90-day mortality was similar in both groups (2%). The authors concluded that LPD offers equal perioperative safety with the reduction in the length of hospital stay in experienced hands. However, the clinical benefit of LPD over OPD was marginal, despite extensive procedural expertise and future research should focus to identify patient groups who would benefit most from LPD (49).

Apart from the above RCTs, several other retrospective studies have evaluated outcomes of MIPD. A propensity-matched analysis by Nassour *et al.*, with a larger number of patients (OPD, n=1,002; MIPD, n=334) demonstrated longer operative time and a lower rate of prolonged length of stay (>14 days) with MIPD. However, readmission rate was higher with MIPD (19.2% *vs.* 14.3%; P=0.04). The rate of 30-day mortality (MIPD 1.8% *vs.* OPD 1.3%; P=0.51), overall complications, POPF, and delayed gastric emptying were comparable (50).

An international, pan-European propensity-matched study included 14 centers (7 countries) performing ≥10 MIPDs annually *vs.* OPD in 53 German/Dutch centers performing ≥10 OPDs annually. The primary outcome measure was 30-day major morbidity. Of the total 4,220 patients, 729 MIPDs were compared with 729 OPDs. The MIPD group included patients with LPD, RPD, and hybrid procedures. No differences were observed in 30-day major morbidity, mortality, and length of stay between MIPD and OPD. However, MIPD was associated with a 10% higher rate of grade B/C POPF. Even after sensitivity analysis, adding pancreatic duct diameter, histopathological diagnosis, and T-stage as propensity score matching variables, the association of higher POPF remained with MIPD. This finding has not been reported in the other larger studies or systematic reviews and warrants prospective evaluation in RCT. Since the etiology of POPF is complex and is known to vary according to the fistula risk score, surgeon experience, and annual case volumes, the impact of minimally invasive technique needs to be compared separately with the open technique (51). With three of the four published RCTs having hospital stay as the primary outcome measure and the rest of the larger systematic reviews and meta-analyses with other short-term measures such as mortality or major morbidity but not POPF as the primary measure, insufficient balance between groups at baseline (residual confounding) could likely have resulted in lack of detection of any difference in POPF between MIPD and OPD in these studies.

Robotic pancreaticoduodenectomy (RPD)

Due to the inherent advantages of the robotic platforms over laparoscopy, RPD became increasingly popular since its first description in 2003 (52). In general, the available retrospective data thus far shows comparable perioperative and short-term oncological outcomes with RPD, LPD, and OPD.

A large, nonrandomized, multi-institutional study by Zureikat *et al.* compared 211 RPDs with 817 OPDs for perioperative outcomes (53). The study demonstrated that post-learning curve, RPD, and OPD are comparable in safety and short-term oncologic efficacy. However, OPD patients had a higher percentage of PDAC cases and a greater proportion of non-dilated (<3 mm) pancreatic ducts. RPD was associated with longer operative times, reduced blood loss, and a smaller number of major complications.

Another large cohort study using US nationwide database, with more than 22,000 operated patients with predominant PDAC histology, compared OPD with MIPD (LPD/RPD) for short and long-term outcomes over 5 years (2010–2015) (54). Several important observations were noted in this study. The utilization of MIPD was in 17% of patients in the US, across the low and high-volume centers. The 90-day mortality and unplanned 30-day readmissions were equivalent between MIPD and OPD. Mortality, despite being comparable in the groups, was high (6.7% in OPD and 5% in the LPD). A high annual hospital volume of PD and high hospital volume of MIPD was independently associated with a significant decrease in 90-day mortality. With the intention to treat design, all MIPD patients who underwent conversion to open surgery were also included. A high conversion rate of 15% with RPD and 25% with LPD was noted. RPD cases that required conversion had a significantly increased odds of 90-day mortality (OR, 3.99; 95% CI: 1.27–12.51) as compared to the completed RPD cases. LPD cases that required conversion to open did not show any higher odds for mortality. Of concern, 38.6% of OPDs and 35.6% of MIPDs were performed at low-volume centers, despite a known inverse PD hospital volume and mortality association, which was also confirmed in this study. R0 resection, lymph nodes yield, and receipt of adjuvant chemotherapy were equivalent between the groups.

A recent network meta-analysis by Kabir *et al.*, compared outcomes after LPD, RPD, and OPD. Four RCTs and 23 propensity-score matched (PSM) studies including a total of 4,945 patients were analyzed. OPD was associated with significantly reduced operative time as compared to LPD and RPD. Four RCTs and 22 PSM studies found that patients who underwent LPD had significantly shorter hospital stays compared with OPD (OR 0.43, 95% CI: 0.28–0.95). Hospital stay was not different after RPD *vs.* LPD, and RPD *vs.* OPD (55). Intraoperative blood loss and postoperative delayed gastric emptying were reduced after LPD and RPD as compared to OPD. RPD was associated with fewer rates of wound infection compared to OPD. The other perioperative outcomes were comparable and the R0 resection rate and lymph node yield were also similar in the three approaches. The authors concluded that when LPD and RPD are performed in high-volume centers, short-term perioperative and oncologic outcomes are largely comparable with traditional OPD, at the expense of longer operating times.

Learning curve (LC)

As discussed previously, MIPD requires significant learning and a dedicated approach. A recent systemic review, that included pooled analysis of 32 studies concluded that overall LC of LPD was comparable to RPD (34 *vs.* 36 cases) (39). The study also highlighted that single surgeon LC of LPD was significantly higher (49 *vs.* 28 cases), whereas institutional LC was higher for RPD as compared to LPD (43 *vs.* 21 cases). Some studies have highlighted relatively shorter LC of RPD, attributable to ergonomic advantages and depth perception of the robotic systems. However, in the studies evaluating LC of RPD a large proportion of surgeons had prior familiarity with laparoscopic surgery and these studies were performed in second decade of the 21st century that corresponds to the period of near stability on the IDEAL paradigm of surgical innovation. Although most of the studies highlight operative time and estimated blood loss as surrogate markers of LC, optimal intraoperative and postoperative outcomes may be equally important markers to study the LC for MIPD.

The evidence-based Miami International guidelines on MIPR are built on studies involving more than 8,500 patients (56). These guidelines represent a pathway for evaluation, dissemination, and propagation of MIPR. By identifying the unmet needs for MIPR, multi-institutional registries, appropriate accreditation of hospitals and institutions along with multicentre clinical trials have been suggested. The guidelines have made strong recommendations for MIDP, however have reinforced the impact of factors like age, BMI, tumor size, pancreatitis on the outcomes and have suggested multi-institutional studies to evaluate the impact of these factors. Numerous issues have also been pointed out with the lack of high-level prospective data, lack of data for MIPR with vascular resections, cost-effectiveness, quality of life, and instrumentation issues. The guidelines have also highlighted the importance of surgical rescue from the bleeding event, the need for well-designed prospective studies to support the use of MIPR in PDAC patients, and the role of MIPR post neoadjuvant treatment. These guidelines represent the highest methodological standards and address all important issues regarding implementation, controversies, and performance of MIPR in the present scenario and its propagation in the future.

Thus, MIPD is safe in experienced hands in high-volume centers and offers almost equivalent, if not better, perioperative outcomes. The short-term oncological outcomes are also similar; however, the majority of the studies lack analysis and comparison of the long-term outcomes. Although the R0 resection and lymph node yield can be considered as surrogate markers for long-term outcomes, these findings must be confirmed in larger studies including patients with PDAC alone, with overall- and disease-free survival as primary outcome measures.

Oncological outcomes (*Table 3*)

None of the RCTs could assess long-term oncological outcomes especially with very few included patients with PDAC. The majority of evidence for long-term outcomes is from retrospective studies, propensity-matched analysis, and systematic reviews (*Table 3*) (57-66). A recent large systematic review by Kamarajah *et al.* included 31 studies with 58,622 patients with periampullary tumors i.e., ampullary, distal bile duct, duodenal, pancreatic. MIPD was performed in 14.9% while 85.1% underwent OPD. Pooled analysis revealed similar 5-year overall survival after MIPD compared with OPD (HR 0.78, 95% CI: 0.50–1.22, P=0.2). A subset analyses for PDAC demonstrated similar 5-year overall survival after MIPD compared with OPD (HR 0.69, 95% CI: 0.32–1.50, P=0.3) (68).

A study by Girgis *et al.*, specifically evaluated oncological outcomes of PDAC, comparing robotic and open approaches. A total of 456 Patients undergoing PD, DP, or distal pancreatectomy and celiac axis resection (DP-CAR) were included with the majority of patients being with PD (n=361). R0 margin status was similar, robotic pancreatectomy patients had a shorter length of stay and reduced wound infection rate. Overall survival for the entire cohort of patients was 24.6 months. The robotic cohort had improved median overall survival nearly reaching statistical significance (25.6 *vs.* 23.9 months; P=0.055) (66).

A propensity-matched analysis by Kwon *et al.* performed a retrospective review of patients undergoing MIPD and OPD for PDAC. A data of 1,048 patients were evaluated with 7.2% patients undergoing MIPD. After PSM, 73 patients undergoing MIPD were matched with 219 patients undergoing OPD. Adjuvant treatment rates were higher following MIPD (80.8% *vs.* 59.8%, P=0.002). The median overall survival and disease-free survival rates were similar between the groups (67).

With the available data, MIPD largely remains investigational and the majority of PDs are performed by conventional open technique. Presently, two ongoing RCTs aim to compare MIPD and OPD with time to functional recovery as a primary endpoint in both these trials (*Table 2*).

PORTAL trial, from China, is a multicenter, non-inferiority, phase III trial comparing robot-assisted versus open PD for benign and malignant lesions of the pancreatic head. Apart from the functional outcomes, the secondary outcome measures will be costs, mortality, overall complication rates, oncological outcomes, and quality of life. The calculated sample size is 244 patients and the results of this trial are expected by 2024.

The second ongoing RCT is from Johns Hopkins comparing MIPD (robot-assisted and laparoscopy) with OPD. Patients with benign, premalignant, or resectable malignant tumors are eligible for inclusion. The estimated

Table 3 Oncological and perioperative outcomes of minimally invasive *vs.* open pancreaticoduodenectomy for pancreatic cancer

Authors/year	Procedure/numbers	Propensity matching	Oncological outcomes								Per-operative outcomes							
			R0 resection (%)	P value	LN harvest	P value	Overall survival (months)	P value	Adjuvant chemotherapy (%)	P value	Operative time (min)	P value	Blood loss (mL)	P value	Hospital stay (days)	P value	Post-operative complication	P value
Croome *et al.* 2014 (57)	Lap/Open; 108/214	–	77/76.6	NS	21.4±8.1; 20.1±7.5	NS	MST 25 months; 21.8 months	NS	76; 76	NS	379.4±93.5; 387.6±91.8	NS	492.4±519.3; 866.7±733.7	0.001	6 [4–118]; 9 [5–73]	<0.001	5.6% *vs.* 13.6%	NS
Sharpe *et al.* 2015 (58)	Lap/Open; 384/4,037	–	80/74	0.02	18±9.7; 16±9.6	0.008	–	–	–	–	–	–	–	–	10±8.0; 12±9.7	<0.0001	–	–
Nussbaum *et al.* 2016 (59)	MIS (Lap &Robotic)/Open; 1,191/6,776	–	79.8/77.9	NS	17.4±10.0; 16.5±9.6	<0.01	2 yr OS 43%; 2 yr OS 47%	NS	55.3; 52.7	NS	–	–	–	–	11.4±10.3; 12.3±9.5	<0.01	–	–
Staufer *et al*. *et al.* 2017 (60)	Lap/Open; 58/193	–	84.5/79.8	NS	27 [9–70]; 17 [1–63]	<0.001	MST;18.5 *vs.* 20.3 months	NS	75.9; 73.5	NS	518 [313–761]; 375 [159–681]	<0.001	250 [50–8,500]; 600 [50–7,800]	0.001	6 [4–68]; 9 [4–71]	<0.001	53% *vs.* 66%	NS
Kantor *et al.* 2017 (61)	Lap/Open; 828/7,385	–	79.1/76.8	NS	18.1±9.5; 17.1±9.6	0.01	MST;20.7 *vs.* 20.9 months	NS	61.4; 60.4	NS	–	–	–	–	10.2±8.5; 11.8±9.3	<0.01	–	–
Chapman *et al.* 2018 (62)	Lap/Open; 248/1,520	–	77.4/73	NS	–	–	MST;19.8 *vs.* 15.6 months	0.02	35.9; 36	NS	–	–	–	–	10 [7–15]; 10 [7–15.5]	0.06	–	–
Kuesters *et al.* 2018 (63)	Lap/Open; 62/278	–	87/71	0.01	17 [7–28]; 16 [2–47]	NS	5 yr OS 20%; 5 yr OS 14%	NS	–	–	477 [295–686]; 428 [245–714]	<0.001	–	–	14 [7–39]; 16 [5–379]	0.03	53% *vs.* 55%	NS
Zhou *et al.* 2019 (64)	Lap/Open; 55/93	Yes	100/94.6	NS	18 [13–25]; 11 [7–14.5]	0.001	MST; 20 *vs.* 18.7 months	NS	47.3; 50.5	NS	330 [260–360]; 260 [07.5– 325.5]	<0.001	150 [100–200]; 200 [150–350]	0.001	13 [11–20]; 14 [10–20]	NS	49% *vs.* 71%	0.008
Choi *et al.* 2020 (65)	Lap/Open; 27/34	–	92.5/70.5	NS	13.33±9.21; 20.65±9.47	NS	MST;44.6 *vs.* 45.2 months	NS	77.7; 79.4	NS	477.7±60.75; 471.21±78.62	NS	232.59±178.68; 448.82±343.83	0.003	21.19±11.13; 19.94±9.79	NS	–	–
Girgis *et al.* 2021 (66)	Robotic/Open; 226/330	–	21.3/18	NS	25.7±11.5; 31.7±13.8	0.0001	MST, 25 *vs.* 23 months	0.055	90.7/89.2	NS	403±125; 353±109	0.0001	–	–	7 *vs.* 9	0.001	32% *vs.* 12% (wound infection)	0.0001
Kwon *et al.* 2020 (67)	MIPD/Open; 76/972	Yes	75/71	NS	18.6±9.9; 22±10.6	0.006	MST, 25 *vs.* 23 months	0.055	79; 68	0.001	392±96; 368±99	0.04	–	–	12±5.5; 15±8.6	0.001	30% *vs.* 35.0%	0.3

MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy; LDP, laparoscopic distal pancreatectomy; RDP, robot-assisted distal pancreatectomy; MIPD, minimally invasive pancreatoduodenectomy; OPD, open pancreatoduodenectomy; LPD, laparoscopic pancreatoduodenectomy; RPD, robot-assisted pancreatoduodenectomy.

sample size is 240 patients and this trial too is expected to be completed in 2024.

Minimally invasive vascular resections for PDAC

A few high-volume experienced pancreatic surgery centers have adopted a minimally invasive approach for pancreatectomies with vascular resections. In a systematic review of 9 studies involving 140 patients of PD with venous resections, 50% of the resections were performed robotically (69). About 60% of these resections were lateral resections requiring primary suture closure or patch closure. In the largest series of PD with vein resections by Beane *et al.* (70), only 1 out of 50 patients underwent segmental vein resection, whereas in a series by Croome, 9 of 22 patients underwent laparoscopic segmental vein resections (71). Segmental vein resections may sometimes need extensive mesenteric vein mobilization and prolonged vein clamping that may result in small bowel edema obscuring laparoscopic vision. The postoperative mortality rate of 0-8% is comparable to open surgery along with comparable blood loss and operative time. The results of these studies indicate that PD with venous resections may be considered feasible in hands of highly experienced surgeons, although any advantage of this approach over open procedure remains to be determined. There are centre-specific case reports and series that mention the technical feasibility of Robotic and Laparoscopic DP-CAR, but guidelines do not recommend minimally invasive surgery in left-sided pancreatic resections with vascular resections (56).

Cost

One of the limitations associated with MIPR is a higher operative cost which has significantly hampered its widespread implementation, particularly the robotic platform. Increased operative costs are attributed to higher equipment cost and the operating room expenditure. A few European and other studies suggest an absolute increase in the cost of more than 6,000 Euros in RPD as compared to OPD (31,33,72,73). However, when the robotic assistance cost is negated, the overall post-operative cost can be significantly less. When post-operative recovery, hospital stay, and quality of life are cumulatively considered, the increase in the cost of MIPR by the robotic platform may not be inhibitory (31,33). The cost-effectiveness of MIPR has been studied in many original articles in the last decade. All these studies have consistently reported higher 'operative' costs and lower 'postoperative' costs in MIPR as compared to open resections resulting in similar cost-effectiveness. It becomes imperative to point out that most of this data is from high volume centres. In an evaluation of a national database for cost-effectiveness of laparoscopic pancreaticoduodenectomy, Tran *et al.* reported shorter hospital stay resulting in lower median charges in high volume centres as compared to the low volume centres. So, the current cost-effective analysis may not be applicable to the low volume centres (74). Moreover, evaluation of a new intervention should include the quality-of-life measurements along with the cost which helps to determine the 'value' of the intervention i.e., health outcomes per unit currency spent. Present studies are deficient in value based analysis and it is premature to conclude MIPR as a valuable intervention at the healthcare level. Although results are suggestive of cost saving trends with MIPR, rigorous value-based analysis strategies in well-designed prospective controlled trials are needed to study the real cost-effectiveness of MIPR (75,76).

Future directions and conclusions

Balancing indications and learning curve is the foremost issue for optimal utilization of MIPR in pancreatic cancer at present. Unpredictable conversions have been linked to increased mortality; therefore, strict indication assessment is needed. Learning curve needs to be optimized, for which at least 10 complex MIPR per year are recommended. Furthermore, the application of artificial intelligence may optimize mentorship and propagate training.

To conclude the development of MIPR for pancreatic cancer will continue to proceed further. Even though the feasibility and the safety of MIPR has been largely established, MIPR for PDAC remains controversial owing to a dearth of the literature evaluating long-term outcomes. Apart from that, the exact indications, appropriate patient selection, enhanced cost, and learning curve issues also need further assessment. Considering the ongoing impact of neoadjuvant treatment on pancreatic cancer surgery and a corresponding increase in vascular resections and arterial divestment procedures, the application of MIPR in these scenarios also remains to be explored. Large multicentric RCTs by high volume pancreatic centres across the countries need to evaluate these controversial issues regarding MIPR for PDAC.

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References

1. Kim HH, Han SU, Kim MC, et al. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival Among Patients With Stage I Gastric Cancer: The KLASS-01 Randomized Clinical Trial. JAMA Oncol 2019;5:506-13.
2. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-8.
3. Park JW, Kang SB, Hao J, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): 10-year follow-up of an open-label, non-inferiority, randomised controlled trial. Lancet Gastroenterol Hepatol 2021;6:569-77.
4. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. Surg Endosc 1994;8:408-10.
5. Cuschieri A. Laparoscopic Pancreatic Resections. Semin Laparosc Surg 1996;3:15-20.
6. Joseph B, Morton JM, Hernandez-Boussard T, et al. Relationship between hospital volume, system clinical resources, and mortality in pancreatic resection. J Am Coll Surg 2009;208:520-7.
7. Strasberg SM, Drebin JA, Linehan D. Radical antegrade modular pancreatosplenectomy. Surgery 2003;133:521-7.
8. Mitchem JB, Hamilton N, Gao F, et al. Long-term results of resection of adenocarcinoma of the body and tail of the pancreas using radical antegrade modular pancreatosplenectomy procedure. J Am Coll Surg 2012;214:46-52.
9. Korrel M, Lof S, van Hilst J, et al. Predictors for Survival in an International Cohort of Patients Undergoing Distal Pancreatectomy for Pancreatic Ductal Adenocarcinoma. Ann Surg Oncol 2021;28:1079-87.
10. de Rooij T, van Hilst J, van Santvoort H, et al. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded Randomized Controlled Trial. Ann Surg 2019;269:2-9.
11. Cuschieri A. Laparoscopic surgery of the pancreas. J R Coll Surg Edinb 1994;39:178-84.
12. Björnsson B, Larsson AL, Hjalmarsson C, et al. Comparison of the duration of hospital stay after laparoscopic or open distal pancreatectomy: randomized controlled trial. Br J Surg 2020;107:1281-8.
13. Korrel M, Vissers FL, van Hilst J, et al. Minimally invasive versus open distal pancreatectomy: an individual patient data meta-analysis of two randomized controlled trials. HPB (Oxford) 2021;23:323-30.
14. Kooby DA, Hawkins WG, Schmidt CM, et al. A multicenter analysis of distal pancreatectomy for adenocarcinoma: is laparoscopic resection appropriate? J Am Coll Surg 2010;210:779-85, 786-7.

15. Magge D, Gooding W, Choudry H, et al. Comparative effectiveness of minimally invasive and open distal pancreatectomy for ductal adenocarcinoma. JAMA Surg 2013;148:525-31.
16. Hu M, Zhao G, Wang F, et al. Laparoscopic versus open distal splenopancreatectomy for the treatment of pancreatic body and tail cancer: a retrospective, mid-term follow-up study at a single academic tertiary care institution. Surg Endosc 2014;28:2584-91.
17. Rehman S, John SK, Lochan R, et al. Oncological feasibility of laparoscopic distal pancreatectomy for adenocarcinoma: a single-institution comparative study. World J Surg 2014;38:476-83.
18. Lee SH, Kang CM, Hwang HK, et al. Minimally invasive RAMPS in well-selected left-sided pancreatic cancer within Yonsei criteria: long-term (>median 3 years) oncologic outcomes. Surg Endosc 2014;28:2848-55.
19. Shin SH, Kim SC, Song KB, et al. A comparative study of laparoscopic vs. open distal pancreatectomy for left-sided ductal adenocarcinoma: a propensity score-matched analysis. J Am Coll Surg 2015;220:177-85.
20. Sulpice L, Farges O, Goutte N, et al. Laparoscopic Distal Pancreatectomy for Pancreatic Ductal Adenocarcinoma: Time for a Randomized Controlled Trial? Results of an All-inclusive National Observational Study. Ann Surg 2015;262:868-73; discussion 873-4.
21. Sharpe SM, Talamonti MS, Wang E, et al. The laparoscopic approach to distal pancreatectomy for ductal adenocarcinoma results in shorter lengths of stay without compromising oncologic outcomes. Am J Surg 2015;209:557-63.
22. Zhang M, Fang R, Mou Y, et al. LDP vs ODP for pancreatic adenocarcinoma: a case matched study from a single-institution. BMC Gastroenterol 2015;15:182.
23. Stauffer JA, Coppola A, Mody K, et al. Laparoscopic Versus Open Distal Pancreatectomy for Pancreatic Adenocarcinoma. World J Surg 2016;40:1477-84.
24. Anderson KL Jr, Adam MA, Thomas S, et al. Impact of minimally invasive vs. open distal pancreatectomy on use of adjuvant chemoradiation for pancreatic adenocarcinoma. Am J Surg 2017;213:601-5.
25. Plotkin A, Ceppa EP, Zarzaur BL, et al. Reduced morbidity with minimally invasive distal pancreatectomy for pancreatic adenocarcinoma. HPB (Oxford) 2017;19:279-85.
26. Kantor O, Bryan DS, Talamonti MS, et al. Laparoscopic Distal Pancreatectomy for Cancer Provides Oncologic Outcomes and Overall Survival Identical to Open Distal Pancreatectomy. J Gastrointest Surg 2017;21:1620-5.
27. Bauman MD, Becerra DG, Kilbane EM, et al. Laparoscopic distal pancreatectomy for pancreatic cancer is safe and effective. Surg Endosc 2018;32:53-61.
28. Raoof M, Ituarte PHG, Woo Y, et al. Propensity score-matched comparison of oncological outcomes between laparoscopic and open distal pancreatic resection. Br J Surg 2018;105:578-86.
29. van Hilst J, de Rooij T, Klompmaker S, et al. Minimally Invasive versus Open Distal Pancreatectomy for Ductal Adenocarcinoma (DIPLOMA): A Pan-European Propensity Score Matched Study. Ann Surg 2019;269:10-7.
30. Melvin WS, Needleman BJ, Krause KR, et al. Robotic resection of pancreatic neuroendocrine tumor. J Laparoendosc Adv Surg Tech A 2003;13:33-6.
31. Xu SB, Jia CK, Wang JR, et al. Do patients benefit more from robot assisted approach than conventional laparoscopic distal pancreatectomy? A meta-analysis of perioperative and economic outcomes. J Formos Med Assoc 2019;118:268-78.
32. Daouadi M, Zureikat AH, Zenati MS, et al. Robot-assisted minimally invasive distal pancreatectomy is superior to the laparoscopic technique. Ann Surg 2013;257:128-32.
33. Lyman WB, Passeri M, Sastry A, et al. Robotic-assisted versus laparoscopic left pancreatectomy at a high-volume, minimally invasive center. Surg Endosc 2019;33:2991-3000.
34. Zhao W, Liu C, Li S, et al. Safety and efficacy for robot-assisted versus open pancreaticoduodenectomy and distal pancreatectomy: A systematic review and meta-analysis. Surg Oncol 2018;27:468-78.
35. Niu X, Yu B, Yao L, et al. Comparison of surgical outcomes of robot-assisted laparoscopic distal pancreatectomy versus laparoscopic and open resections: A systematic review and meta-analysis. Asian J Surg 2019;42:32-45.
36. Nassour I, Winters SB, Hoehn R, et al. Long-term oncologic outcomes of robotic and open pancreatectomy in a national cohort of pancreatic adenocarcinoma. J Surg Oncol 2020;122:234-42.
37. de Rooij T, van Hilst J, Boerma D, et al. Impact of a Nationwide Training Program in Minimally Invasive Distal Pancreatectomy (LAELAPS). Ann Surg 2016;264:754-62.
38. Dokmak S, Ftériche FS, Aussilhou B, et al. The Largest European Single-Center Experience: 300 Laparoscopic Pancreatic Resections. J Am Coll Surg 2017;225:226-234.e2.
39. Chan KS, Wang ZK, Syn N, et al. Learning curve of laparoscopic and robotic pancreas resections: a systematic

review. Surgery 2021;170:194-206.
40. Ohtsuka T, Ban D, Nakamura Y, et al. Difficulty scoring system in laparoscopic distal pancreatectomy. J Hepatobiliary Pancreat Sci 2018;25:489-97.
41. Deiro G, De Pastena M, Paiella S, et al. Assessment of difficulty in laparoscopic distal pancreatectomy: A modification of the Japanese difficulty scoring system - A single-center high-volume experience. J Hepatobiliary Pancreat Sci 2021;28:770-7.
42. van Hilst J, Korrel M, de Rooij T, et al. Oncologic outcomes of minimally invasive versus open distal pancreatectomy for pancreatic ductal adenocarcinoma: A systematic review and meta-analysis. Eur J Surg Oncol 2019;45:719-27.
43. Strobel O, Hank T, Hinz U, et al. Pancreatic Cancer Surgery: The New R-status Counts. Ann Surg 2017;265:565-73.
44. Sanjay P, Takaori K, Govil S, et al. 'Artery-first' approaches to pancreatoduodenectomy. Br J Surg 2012;99:1027-35.
45. Ironside N, Barreto SG, Loveday B, et al. Meta-analysis of an artery-first approach versus standard pancreatoduodenectomy on perioperative outcomes and survival. Br J Surg 2018;105:628-36.
46. Palanivelu C, Senthilnathan P, Sabnis SC, et al. Randomized clinical trial of laparoscopic versus open pancreatoduodenectomy for periampullary tumours. Br J Surg 2017;104:1443-50.
47. Poves I, Burdío F, Morató O, et al. Comparison of Perioperative Outcomes Between Laparoscopic and Open Approach for Pancreatoduodenectomy: The PADULAP Randomized Controlled Trial. Ann Surg 2018;268:731-9.
48. van Hilst J, de Rooij T, Bosscha K, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. Lancet Gastroenterol Hepatol 2019;4:199-207.
49. Wang M, Li D, Chen R, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours: a multicentre, open-label, randomised controlled trial. Lancet Gastroenterol Hepatol 2021;6:438-47.
50. Nassour I, Wang SC, Christie A, et al. Minimally Invasive Versus Open Pancreaticoduodenectomy: A Propensity-matched Study From a National Cohort of Patients. Ann Surg 2018;268:151-7.
51. Mungroop TH, van Rijssen LB, van Klaveren D, et al. Alternative Fistula Risk Score for Pancreatoduodenectomy (a-FRS): Design and International External Validation. Ann Surg 2019;269:937-43.
52. Giulianotti PC, Coratti A, Angelini M, et al. Robotics in general surgery: personal experience in a large community hospital. Arch Surg 2003;138:777-84.
53. Zureikat AH, Postlewait LM, Liu Y, et al. A Multi-institutional Comparison of Perioperative Outcomes of Robotic and Open Pancreaticoduodenectomy. Ann Surg 2016;264:640-9.
54. Torphy RJ, Friedman C, Halpern A, et al. Comparing Short-term and Oncologic Outcomes of Minimally Invasive Versus Open Pancreaticoduodenectomy Across Low and High Volume Centers. Ann Surg 2019;270:1147-55.
55. Kabir T, Tan HL, Syn NL, et al. Outcomes of laparoscopic, robotic, and open pancreatoduodenectomy: A network meta-analysis of randomized controlled trials and propensity-score matched studies. Surgery 2022;171:476-89.
56. Asbun HJ, Moekotte AL, Vissers FL, et al. The Miami International Evidence-based Guidelines on Minimally Invasive Pancreas Resection. Ann Surg 2020;271:1-14.
57. Croome KP, Farnell MB, Que FG, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? Ann Surg 2014;260:633-8; discussion 638-40.
58. Sharpe SM, Talamonti MS, Wang CE, et al. Early National Experience with Laparoscopic Pancreaticoduodenectomy for Ductal Adenocarcinoma: A Comparison of Laparoscopic Pancreaticoduodenectomy and Open Pancreaticoduodenectomy from the National Cancer Data Base. J Am Coll Surg 2015;221:175-84.
59. Nussbaum DP, Adam MA, Youngwirth LM, et al. Minimally Invasive Pancreaticoduodenectomy Does Not Improve Use or Time to Initiation of Adjuvant Chemotherapy for Patients With Pancreatic Adenocarcinoma. Ann Surg Oncol 2016;23:1026-33.
60. Stauffer JA, Coppola A, Villacreses D, et al. Laparoscopic versus open pancreaticoduodenectomy for pancreatic adenocarcinoma: long-term results at a single institution. Surg Endosc 2017;31:2233-41.
61. Kantor O, Talamonti MS, Sharpe S, et al. Laparoscopic pancreaticoduodenectomy for adenocarcinoma provides short-term oncologic outcomes and long-term overall survival rates similar to those for open pancreaticoduodenectomy. Am J Surg 2017;213:512-5.
62. Chapman BC, Gajdos C, Hosokawa P, et al. Comparison of laparoscopic to open pancreaticoduodenectomy in elderly patients with pancreatic adenocarcinoma. Surg Endosc 2018;32:2239-48.

63. Kuesters S, Chikhladze S, Makowiec F, et al. Oncological outcome of laparoscopically assisted pancreatoduodenectomy for ductal adenocarcinoma in a retrospective cohort study. Int J Surg 2018;55:162-6.
64. Zhou W, Jin W, Wang D, et al. Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a propensity score matching analysis. Cancer Commun (Lond) 2019;39:66.
65. Choi M, Hwang HK, Rho SY, et al. Comparing laparoscopic and open pancreaticoduodenectomy in patients with pancreatic head cancer: oncologic outcomes and inflammatory scores. J Hepatobiliary Pancreat Sci 2020;27:124-31.
66. Girgis MD, Zenati MS, King JC, et al. Oncologic Outcomes After Robotic Pancreatic Resections Are Not Inferior to Open Surgery. Ann Surg 2021;274:e262-8.
67. Kwon J, Song KB, Park SY, et al. Comparison of Minimally Invasive Versus Open Pancreatoduodenectomy for Pancreatic Ductal Adenocarcinoma: A Propensity Score Matching Analysis. Cancers (Basel) 2020;12:982.
68. Kamarajah SK, Gujjuri R, Bundred JR, et al. Long-term survival after minimally invasive resection versus open pancreaticoduodenectomy for periampullary cancers: a systematic review, meta-analysis and meta-regression. HPB (Oxford) 2021;23:197-205.
69. Addeo P. Minimally invasive pancreaticoduodenectomy with venous resection: results of a systematic review. Mini-invasive Surgery 2020;4:64.
70. Beane JD, Zenati M, Hamad A, et al. Robotic pancreatoduodenectomy with vascular resection: Outcomes and learning curve. Surgery 2019;166:8-14.
71. Croome KP, Farnell MB, Que FG, et al. Pancreaticoduodenectomy with major vascular resection: a comparison of laparoscopic versus open approaches. J Gastrointest Surg 2015;19:189-94; discussion 194.
72. Higgins RM, Frelich MJ, Bosler ME, et al. Cost analysis of robotic versus laparoscopic general surgery procedures. Surg Endosc 2017;31:185-92.
73. Magge DR, Zenati MS, Hamad A, et al. Comprehensive comparative analysis of cost-effectiveness and perioperative outcomes between open, laparoscopic, and robotic distal pancreatectomy. HPB (Oxford) 2018;20:1172-80.
74. Tran TB, Dua MM, Worhunsky DJ, et al. The First Decade of Laparoscopic Pancreaticoduodenectomy in the United States: Costs and Outcomes Using the Nationwide Inpatient Sample. Surg Endosc 2016;30:1778-83.
75. Conlon KC, de Rooij T, van Hilst J, et al. Minimally invasive pancreatic resections: cost and value perspectives. HPB (Oxford) 2017;19:225-33.
76. Joechle K, Conrad C. Cost-effectiveness of minimally invasive pancreatic resection. J Hepatobiliary Pancreat Sci 2018;25:291-8.

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