Laparoscopic pancreatoduodenectomy: a narrative review of the feasibility and outcomes

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Background and Objective: Pancreatoduodenectomy is the standard procedure for resection of periampullary malignancies. It is a technically complex procedure requiring extensive experience in hepatopancreatobiliary resections and previous data have demonstrated a strong relationship between case volume and outcomes. While laparoscopic approaches have been adopted for other major intra-abdominal resections, pancreatoduodenectomy remains most commonly performed with an open technique due to the technical complexity of the procedure and the steep learning curve. We reviewed the available literature on the outcomes between open (OPD) and laparoscopic (LPD) pancreatoduodenectomy.

Methods: A search was conducted in PubMed, Medline, and Cochrane Review databases to identify retrospective and prospective studies comparing outcomes of OPD *vs.* LPD from 2010 to 2022. We utilized the phrases "minimally invasive", "laparoscopic", "pancreatoduodenectomy", and "Whipple".

Key Content and Findings: We identified retrospective and prospective studies evaluating the difference of LPD *vs.* OPD. To date, four randomized control trials have been conducted to evaluate outcome differences. LPD remains an uncommon procedure, with reports available mainly from high volume centers. LPD requires longer operating time, and patients tend to have shorter lengths of stay, and comparable oncologic outcomes to OPD. The evidence for functional recovery, estimated blood loss, complications, and survival is less consistent across studies.

Conclusions: LPD is a feasible procedure; however, the data are largely inconsistent across studies, likely due to the rarity with which the procedure is performed in the surgical community.

Keywords: Laparoscopy; minimally invasive; pancreatoduodenectomy; Whipple

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Introduction

Background

Pancreatoduodenectomy (PD) is a complex surgical procedure performed to resect benign and malignant periampullary lesions. The technical complexity of pancreatic head resections is due to its anatomical proximity to major structures in the retroperitoneum, including the superior mesenteric artery and superior mesenteric vein/portal vein, inferior vena cava, and the porta hepatis, and the delicate reconstruction required to re-establish biliary and pancreatic continuity with the bowel (1). The technical difficulty can be further exacerbated by inflammatory or fibrotic changes that develop as a sequela of preoperative interventions and pancreatitis (2).

Resection is the only potential cure available for malignant periampullary diseases, including pancreatic ductal adenocarcinoma, distal cholangiocarcinoma, duodenal

Table 1 Search summary

Items	Specification
Date of search	08/14/2022
Databases and other sources searched	PubMed, Medline, Cochrane Review
Search terms used	“Minimally invasive” AND “pancreaticoduodenectomy” OR “Laparoscopic” AND “Pancreatoduodenectomy” OR “Minimally Invasive” AND “Whipple” OR “Laparoscopic” AND “Whipple”
Timeframe	01/01/2010–08/01/2022
Inclusion and exclusion criteria	Inclusion: retrospective, meta-analysis, prospective studies reporting outcomes of laparoscopic surgery, English
	Exclusion: inclusion of robotic cases in analysis of minimally invasive surgery cases
Selection process	NK reviewed all identified articles for inclusion and exclusion criteria
	References of articles were further reviewed to identify possible sources

adenocarcinoma, and ampullary adenocarcinoma (1). Performing a safe and effective resection is therefore imperative to improving patient outcomes. The procedure is associated with high rates of morbidity, including postoperative pancreas fistula, delayed gastric emptying, wound infection, hemorrhage, and chyle leak, with overall complications rate reported to be as high as 52%. The relationship between operative volume and outcomes has been well described and the surgeon’s experience in performing this procedure is invaluable to obtaining positive postoperative outcomes (3-6).

Gagner *et al.* first described laparoscopic pancreatoduodenectomy (LPD) in 1994, and in a follow up study concluded that the procedure did not have an advantage compared to open resection due to the high conversion rates (7,8). Ongoing studies have aimed to determine if the minimally invasive approach is comparable to open resections and can improve postoperative recovery without compromising complication rates. Despite this, now 30 years since its first description, LPD has failed to be widely adopted, likely due to the rarity with which the procedure is performed (9,10).

Rationale

To date, four randomized controlled trials (RCTs) have been performed to compare the outcome differences of laparoscopic versus open pancreatoduodenectomy (OPD), with the most recent results becoming available in 2021. To our knowledge, this is the first review to report the collective outcomes of all available randomized studies.

Objective

Utilizing the most up to date evidence, we evaluate the safety, efficacy, and feasibility of LPD compared to OPD. We present the following article in accordance with the Narrative Review reporting checklist (available at https://ales.amegroups.com/article/view/10.21037/ales-22-53/rc).

Methods

A narrative review was performed using PubMed, Medline, and Cochrane Review databases using the following terms: “minimally invasive” AND “pancreatoduodenectomy” OR “laparoscopic” AND pancreatoduodenectomy” OR “minimally invasive” AND “Whipple” OR “laparoscopic” AND “Whipple.” Studies published in English between January 1, 2010 and August 1, 2022 were included for review. The references of acquired sources were reviewed in order to identify other possibly missed studies. Articles that included robotic resections in their analysis were excluded (*Table 1*).

Discussion

Prior to 2017, the majority of the evidence for LPD was derived from single institution retrospective series or matched comparative studies. The first RCT comparing OPD to LPD was performed in 2017 (*Table 2*). While the procedure has been demonstrated to be feasible, the data regarding outcomes, survival, and safety are not consistent across the literature.

Table 2 Randomized controlled trials comparing laparoscopic and open pancreaticoduodenectomy

Variables	PLOT (11)	PADULAP (12)	LEOPARD-2 (13)	Wang *et al.* (14)
Study details				
Year	2017	2018	2019	2021
Design	Single center, non-blinded	Single center, non-blinded	Multicenter, patient-blinded	Multicenter, non-blinded
Sample size	32 LPD, 32 OPD	32 LPD, 29 OPD	50 LPD, 49 OPD	297 LPD, 297 OPD
Inclusion	Age 30–70 years old; malignancies requiring PD	>18 years old; any condition (benign or malignant) requiring PD	>18 years old; any condition (benign or malignant) requiring PD	Age 18–75 years old; any condition (benign or malignant) requiring PD
Exclusion	Unresectable disease at onset or during procedure	Preplanned major vascular resection; rescue surgery after neo-adjuvant treatment; ECOG PS >2; severe chronic cardiac, pulmonary, hepatic, renal disease; hostile abdomen for laparoscopy; pregnancy	Possible major vessel involvement on preoperative imaging; BMI >35 kg/m^2; history of neo-adjuvant radiotherapy	Distant metastasis; ASA >4; synchronous malignancy of other organ, second cancer requiring resection; pregnancy; history of/ or plan for neo-adjuvant chemotherapy
Outcomes				
Operative time (min)				
LPD	359	486	410	325
OPD	320	365	274	300
P value	0.041	<0.0001	<0.0001	<0.0001
Blood loss (mL)				
LPD	250	Not reported	300	200
OPD	401		450	300
P value	<0.001		0.13	<0.0001
Postoperative outcomes				
Overall complications (%)				
LPD	31.0	68.8	50.0	50.0
OPD	25.0	72.5	39.0	46.0
P value	0.752	0.04	0.26	0.29
Length of stay (days)				
LPD	7.0	13.5	12.0	15.0
OPD	13.0	17.0	11.0	16.0
P value	0.001	0.024	0.86	0.02
Readmission (%)				
LPD	6.0	21.8	16.0	3.0
OPD	9.0	13.8	20.0	2.0
P value	0.763	0.05	0.57	0.31

Table 2 (*continued*)

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Variables	PLOT (11)	PADULAP (12)	LEOPARD-2 (13)	Wang *et al.* (14)
Oncologic outcomes				
R0 (%)				
LPD	96.8	59.4	82.0	98.0
OPD	94.0	51.7	76.0	97.0
P value	0.128	0.61	0.35	0.21
Lymph node yield				
LPD	18	15	11	12
OPD	17	21	11	13
P value	0.063	0.17	0.79	0.25
Survival				
90-day mortality (%)				
LPD	Not reported	0	10.0	2.0
OPD		6.9	2.0	2.0
P value		0.20	0.20	0.76

ASA, American Society of Anesthesiologist physical status classification system; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; LPD, laparoscopic pancreatoduodenectomy; OPD, open pancreatoduodenectomy; PD, pancreatoduodenectomy.

Operative outcomes

Operative time

The most consistently reported difference between LPD and OPD is prolonged operating time (15-19). Similar results have been reported in the PADULAP and LEOPARD-2 RCTs where a longer median operative time was reported for the LPD group (460 *vs.* 365 min, P=0.004) and (410 *vs.* 274 minutes, P<0.001), respectively (12,13). As may be expected, multiple retrospective studies have reported a decrease in operating time in the LPD group with increasing surgeon experience (20-23). In a retrospective review of their first 150 LPD cases, Nagakawa *et al.* reported that the operating time only started to decrease after 22–29 cases were performed by the same surgeon (24). As LPD remains a very small percentage of all PD performed (as low as 4% of all PD in a NSQIP review from 2014 to 2016) and the majority of data are derived from single institution or single surgeon experiences, it is likely that wider implementation of LPD will initially require longer operative times than reported and require extensive repetition to establish an operative time comparable to the open approach (25).

Blood loss

Several retrospective studies, RCTs, and a meta-analysis report a decreased estimated blood loss (EBL) associated with LPD (13,19,26-28). The failure of earlier retrospective matched studies to report similar results may be due to the steep learning curve associated with performing the laparoscopic resection and not due to the surgical approach itself (28,29). For example, Dokmak *et al.* in a follow up study reported decrease in EBL in the LPD group compared to their earlier series. This decrease in EBL may be due to a larger sample size, modified patient selection, or improved technique that was acquired with increasing experience (22,29). The results of multiple RCT supports that the laparoscopic approach may be superior in reducing blood loss if performed by surgeons who have overcome the procedural learning curve (12,14,26,30).

Postoperative outcomes

Recovery

A major benefit cited for minimally invasive approaches in other surgical procedures is improved functional recovery (30-32). There is evidence from retrospective studies that LPD results in reduced pain, less analgesic requirements, earlier return of bowel function, and earlier oral intake (28,33-35). However, the patient-blinded RCT LEOPARD-2 trial did not replicate these findings where the LPD group required 10 *vs.* 8 days in the OPD arm to meet the study's definition of functional recovery: pain control with only oral regimen, independent mobility, and the ability to tolerate 50% of daily-required caloric intake. This may be attributed to the study's small sample size or its strict definition of "functional recovery", which likely was not established in retrospective studies (13).

Complications

Safety outcomes are variable across several reports. Major complications including Clavien-Dindo grade (CD) ≥3, pancreatic fistulas, delayed gastric emptying, or postoperative hemorrhage are comparable in several retrospective series (16,19,33). The PLOT trial and the RCT by Wang *et al.* reported a comparable complication rate between the LPD and OPD group, and the PADULAP study reported lower rates of CD <3 complications in the LPD group (11,12,14). Croome *et al.*, in their single surgeon experience from 2008 to 2013 of 108 LPD, identified a significant lower rate of delayed gastric emptying in the LPD group (9% *vs.* 18%) (36). Alternatively, Nieuwenhujius reported that 7 of the first 10 LPD cases (70%) in their retrospective institutional review had anastomosis-related complications *vs.* only 16% in the OPD group. This high surgical complication rate led the group to transition to a hybrid approach where the reconstruction was performed through a small laparotomy incision (37). Similarly, Wang *et al.*, in the largest retrospective series consisting of 1,029 LPD cases from 2010 to 2016, reported an overall complication rate of 49.6% with 21% having CD ≥3 complications. This is comparable to the 52% overall complication rate reported for OPD in a large retrospective series of 2,564 resections (6,38). Similarly, a meta-analysis by Nickel *et al.* utilizing results from the PLOT, PADULAP, and LEOPARD-2 trials did not detect a significant difference in postoperative complications such as fistula formation, delayed gastric emptying, hemorrhage, bile leaks or readmissions (39). It is vital to note that despite the comparable postoperative complication rates in in the LEOPARD-2 group, the study was terminated early due to safety concerns as five patients died within 90-day in the LPD arm compared to none in the OPD arm (13). Given these results, one approach does not appear superior to the other in reducing complications.

Length of stay

Shorter length of stay after laparoscopic abdominal surgeries for a wide range of pathologies is well-described (40-43). Several studies report a shorter length of stay for patients who underwent LPD (27-29,36,38,44). This outcome was also reported by multiple randomized control trials. This was most dramatic in the PLOT trial with a median length of stay of 7 days reported for the LPD group *vs.* 13 days for the OPD arm (11). Similarly, the PADULAP study reported a shorter length of stay in the LPD group (median of 13.5 *vs.* 17 days) (12). This outcome should be viewed with caution as both the PLOT and PADULAP trials reported increased frequency of 30-day readmissions for the LPD arm (11,12). Further, the difference in length of stay may be reflective of the institution or surgeon experience as PLOT and PADULAP trials were both single institution studies with 2 surgeons assigned to procedures in the PLOT trial and a single surgeon in the PADULAP trial. In a subsequent study published in 2022, Dokmak *et al.* reported a decreased length of stay in their larger retrospective review of 130 patients, which was not detected in their original publication from 2015 (22,29). This discrepancy may be explained by a larger sample size in the later study, the group's decision to avoid LPD in patients at high risk of forming postoperative pancreatic fistulas, and modifications of their surgical technique (29). Moreover, Tan *et al.* in their retrospective review of 142 LPD *vs.* 93 OPD performed by the same surgeon from 2015 to 2019 did not detect a difference in the length of stay (34), and a review of the NCDB from 2010 to 2011 similarly found no difference in length of hospitalization between the two approaches (44). Taken together, a shorter length of stay after LPD is not a consistent finding, and may reflect institutional practices and surgeon experience more than it does the effect of the surgical approach.

Oncologic outcomes

No major difference has been reported between R0 resections for malignant cancer resected by LPD *vs.* OPD in all four RCT and several retrospective studies (11-14). While there are also reports that R0 rate may be improved by the laparoscopic approach, it is critical to note that these outcomes may be influenced by selection bias for patients with less extensive disease. For example, Delitto *et al.* excluded patients with borderline resectable pancreas cancer from their study, and in the meta-analysis by Jiang *et al.* two of the six studies analyzed for R0 resection rates excluded cases with borderline resectable tumors (26,27).

Similarly, lymph node yield is comparable between the two approaches (11-15,22,26) and several reports have even demonstrated a superiority of LPD for lymph node retrieval (20,27,35,44). While the surgical approach may allow improved lymph node yield, it is also important to consider that increasing experience may also explain this finding. For example, Conroy *et al.* found that increased lymph node harvest occurred in cases performed at high volume centers (9). Additionally, Dokmak *et al.* reported an increase in lymph node retrieval in their follow up study, although they comment that this may be due to technical adjustments specifically implemented in an effort to increase lymph node yield (29).

Survival

The long-term survival benefit of LPD *vs.* OPD is infrequently reported, and most reports focus on post-operative mortality. A large number of studies report similar 90-day survival in the LPD and OPD groups, however the LEOPARD-2 trial was terminated early due to an unacceptable 90-day mortality rate in the laparoscopic arm (9,13,16,20). In the RCT by Wang *et al.*, no difference was detected in 90-day survival (14). Alternatively, Chapman *et al.* demonstrated an improved 90-day survival in the LPD group (45). In the same study, the group reported that patients >75 years old who required conversions to OPD had higher rates of 90-day mortality. This may indicate that 90-day postoperative mortality was reflective of the complexity of the resection and the disease burden, and not solely the surgical approach (45). Improved 90-day survival has been attributed to resections performed at high-volume academic centers and increased surgeon experience (9,38). While Wang *et al.* report that 30-day mortality decreased with increasing number of LPD cases performed, Mazzola *et al.* did not detect a difference in 90-day mortality when comparing their earlier *vs.* later resections from 2017 to 2020 (38,46).

Long-term survival outcomes are not widely reported. Hakeem *et al.* report no difference in overall survival for their series of pancreatic head malignancies of similar underlying biology and grade (47). Alternatively, Stauffer *et al.* reported a 5-year overall survival benefit in the LPD group (32% *vs.* 15%,) however, it is important to note that there was a higher number of patients with T1 tumors in the LPD group (13.8% *vs.* 4.02%, P=0.02) (19). Similarly, Croome *et al.* also reported a longer progression free survival in the LPD group (P=0.03) with 43% recurring in the LPD group *vs.* 53% in the OPD group. Of note, no difference was noted in R0 resections in these two study arms (77.8% LPD *vs.* 76.6% OPD, P=0.8). Of those who recurred, local recurrence occurred more frequently in the OPD group (17% *vs.* 27%, P=0.04). While no difference was found in the number of patients receiving adjuvant chemotherapy, the LPD cohort had a significantly earlier time to initiating adjuvant chemotherapy (48 *vs.* 59 days, P<0.001), and fewer delays (>90 days) to initiating treatment. Based on this, it is unclear if the progression free survival benefit demonstrated by this group is derived from the surgical approach or the adjuvant treatment (36).

Technical approach or surgical experience?—viewing outcomes with caution

It is important to view these results with caution as they are likely more reflective of the skill of a small subset of highly skilled surgeons and may not be generalizable to the wider surgical community (39). The results of PLOT and PADULAP are based on resections performed by individual expert surgeons: 1 in the PLOT trial and 2 in the PADULAP trial (11,12). In the multi-institutional studies by van Hilst *et al.* and Wang *et al.*, the resections were only performed at high volume centers. Even more, the participating surgeons were required to not only have undergone a specific LPD training, but also to have performed at least 20 LPD per year in the study by van Hilst *et al.* and 104 LPD in the study by Wang *et al.* (13,14). It is important to consider this information in the context of practice trends of PD. In fact, only about 5% of surgeons were reported to perform more than 12 OPD per year in a review of outcomes from 2014 to 2016 (4). Even more, of more than 10,000 PD performed in that time frame, only 4% were performed laparoscopically (25). Therefore, while in concept LPD is safe compared to the open procedure, the practicality of its implementation into common surgical practice is unlikely.

Looking forward: robotic PD

Robotic surgery is leading the way of minimally invasive surgery in many surgical fields. The first robotic PD was reported in 2003 (48), while in the last 20 years, the robotic approach has been incorporated in many large pancreatic cancer programs with promising results (49). The advantages of robotic technique over either open or laparoscopic surgery have been well described and include magnified and 3D optics, fine motor and improved range of movement and better ergonomics (50).

According to multiple retrospective studies, specifically in pancreatic resection, the robotic approach might offer lower overall complication rate including fewer wound infections, lower margin positivity rate, and faster postoperative return to activity (51,52), while part of the drawbacks of this approach are the longer operative time, learning curve and significantly higher costs (53-55).

No prospective data or RCT on robot-assisted pancreatic resection are available as of yet but RCT to evaluate the outcomes are ongoing (e.g., PORTAL trial) (56). At current levels of evidence, robotic PD is regarded as a feasible and safe option, with promising results, but cannot be regarded as a superior or safer option than OPD. Further prospective research is necessary to define the role of the robotic approach in PD and should aim to identify the indications in which those subgroups of patients might benefit the most.

Conclusions

LPD is safe when performed by highly skilled and experienced surgeons, but may not be easily integrated into the common practice given the rarity with which it is performed and the expertise it requires. The reported outcomes are inconsistent across the literature, likely due to the small volume of cases, which are often performed by highly-specialized surgeons. To better understand the outcomes of this surgical approach, a larger number of cases performed by more surgeons is necessary, although this may not be practical given the extensive laparoscopic and hepatopancreatobiliary expertise required. Even more, emerging data suggest that the future of minimally invasive pancreatic surgery may be behind the robotic console.

The strengths of our review are inclusion of data from all available RCTs, the largest of which was reported in 2021. Furthermore, this review includes the most up-to-date meta-analysis results and excluded reviews that included robotic resections in their analysis in order to present the most specific LPD data. Our weaknesses lie in not performing our own meta-analysis. Furthermore, while there is a shift to focus on robotic resections, we believe it is critical to review all the available evidence for LPD, which by itself may serve as an impetus to fuel further studies in more technically attainable approaches such as robotic surgery.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://ales.amegroups.com/article/view/10.21037/ales-22-53/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://ales.amegroups.com/article/view/10.21037/ales-22-53/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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