Systematic Review

Open and minimally invasive pancreatic surgery—a review of the literature

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Background: There is increasing evidence demonstrating the safety, feasibility and improved postoperative recovery of laparoscopic pancreas resections. The purpose of this study is to review recent advances in laparoscopic distal pancreatectomy (LDP) and minimally invasive pancreaticoduodenectomy (MIPD) with an emphasis on laparoscopic technique, intraoperative outcomes, perioperative outcomes, and oncologic outcomes.

Methods: A systematic literature search was performed using MEDLINE, Web of Science, and Embase. Studies were included if they were an original series in adult patients comparing laparoscopic and open pancreatectomies between 2005 and 2015 with ten or more patients in the laparoscopic group. Patient demographics and intraoperative, postoperative, and oncologic variables were recorded. Odds ratios (ORs) were calculated from dichotomous data and the mean difference (MD) from the continuous data, both with 95% confidence intervals (CIs).

Results: A total of 495 articles were reviewed, 42 of which were selected and included in the distal pancreatectomy group and 19 studies in the pancreaticoduodenectomy group. LDP was performed in 20.2% (n=3,759/18,587) of patients. MIPD was performed in 14.8% (n=3,692/24,923) of patients. Patients in the LDP group had longer operating times (P<0.001), lower estimated blood loss (P<0.001), reduced number of red blood cell transfusions (P<0.001), higher rate of spleen preservation (P<0.001), lower positive margin (P<0.001), lower overall complication rates (P<0.001), reduced 30-day mortality or in-hospital mortality (P=0.012), less post-operative bleeding (P=0.003), decreased wound infections (P<0.001), shorter length of hospital stay (P<0.001), earlier return of bowel function (P<0.001), quicker time to PO intake (P<0.001), and fewer days of IV narcotics (P=0.016). The LDP group had similar lymph node (LN) retrieval (P=0.325), number of patients with positive LN (P=0.734), pancreatic fistula rates (P=0.539), need for re-operation (P=0.354), readmission rates (P=0.898), and time to ambulation (P=0.081) as the open group. The MIPD group had longer operating room times (P<0.001), fewer intra-operative red blood cell transfusions (P=0.009), lower positive margin rate (P=0.022), increased post-operative bleeding (P=0.024), shorter length of hospital stay (P<0.001), lower readmission rate (P=0.048), earlier return of bowel function (P<0.001), and shorter time to PO intake (P<0.001) in comparison to the open group. However, both groups had similar LN retrieval (P=0.142), number of patients with positive LNs (P=0.099), overall morbidity (P=0.145), 30-day or in-hospital mortality (P=0.853), pancreatic fistula (P=0.685), delayed gastric emptying (DGE) (P=0.092), bile leak (P=0.617), wound infections (P=0.061), and similar reoperation rates (P=0.863).

Conclusions: Analysis of the available literature suggests that laparoscopic pancreatectomies are feasible, safe, and potentially have improved perioperative recovery; while achieving equivalent oncologic outcomes when compared to open resection. Further investigation with randomized controlled trials is needed to avoid selection bias and control for confounding factors inherently found in the studies reviewed. However, this

analysis does suggest a growing acceptance of laparoscopic pancreas surgery.

Keywords: Laparoscopic; minimally invasive; pancreatic resection; tumor; distal pancreatectomy; pancreaticoduodenectomy; Whipple

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Background

Minimally invasive gastrointestinal surgery has demonstrated reduced post-operative pain, shorter hospital stays, rapid return to baseline performance status, and reduced morbidity with oncological equivalent outcomes when compared to the traditional open procedures (1-11). However, adoption of laparoscopy for the pancreas has been slower to evolve due to the retroperitoneal position, proximity of major vascular structures, delicate nature of the organ, technical challenges of reconstruction and tendency for post-operative complications that can result in significant morbidity.

In 1994, Gagner and Pomp described the first laparoscopic pancreaticoduodenectomy in a patient with chronic pancreatitis and concluded that while it was technically feasible, the laparoscopic procedure may not improve the post-operative outcome or shorten the post-operative recovery period (12). In 1996, Gagner and Pomp also reported on their initial experience with laparoscopic distal pancreatectomy (LDP) in patients with islet cell tumors and concluded that laparoscopic resection resulted in shorter hospital recovery and is a feasible alternative to open surgery (13).

Since these first reports there is increasing evidence demonstrating not only the safety and feasibility of laparoscopic pancreatic resection, but that it may also result in enhanced postoperative recovery. Current techniques employed for minimally invasive pancreatic resection include total laparoscopy and robotic-assisted laparoscopy. The purpose of this study is to review and analyze recent advances in LDP and minimally invasive pancreaticoduodenectomy (MIPD) with an emphasis on laparoscopic technique, intraoperative outcomes, perioperative outcomes, and oncologic outcomes.

Methods

Relevant publications were identified by searching the following databases: MEDLINE (via PubMed, Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Ovid MEDLINE Daily), Embase (via Embase.com), and Web of Science. Publication date was limited from January 2005 to articles indexed in the databases as of August 2015. The final search was completed on August 25, 2015. No language limits were applied. Animal studies, comments, editorials, and letters were excluded. The search strategies included the following concepts: "pancreatic neoplasms", "total pancreatectomy", "distal pancreatectomy", and "pancreaticoduodenectomy." Multiple subject headings (including MeSH [Medical Subject Headings] terms in MEDLINE and Emtree terms in Embase) and text words were used to identify each concept and develop the search strategies. The following is an example of the search strategy used in PubMed: *Pancreatic cancer concept* = (pancrea* AND (cancer* OR tumor* OR tumour* OR neoplas* OR carcinoma* OR adenocarcinoma* OR cholangiocarcinoma* OR malignan* OR oncolog*)) OR "Pancreatic Neoplasms"[Mesh] OR ("Pancreas"[Mesh] AND "Neoplasms"[Mesh]); *pancreaticoduodenectomy concept* = (whipple* OR pancreaticoduodenectom* OR pancreatoduodenectom* OR "Pancreaticoduodenectomy"[Mesh]) AND open AND (laparoscop* OR "minimally invasive"); *distal pancreatectomy concept* = (pancreatectom* OR splenopancreatectom* OR "Pancreatectomy"[Mesh]) AND (distal OR left) AND open AND (laparoscop* OR "minimally invasive"); *total pancreatectomy concept* = (pancrea* AND resect*) OR pancreatectom* OR splenopancreatectom* OR "Pancreatectomy"[Mesh]) AND total AND open AND (laparoscop* OR "minimally invasive").

Relevant articles identified by cross-referencing were also reviewed. Studies were included only if they were original series in adult patients comparing laparoscopic and open distal pancreatectomy or pancreaticoduodenectomy in the English language. Hand-assisted techniques were excluded. The laparoscopic group included at least 10 patients to minimize the effect of the learning curve for the technique.

Patients were also excluded if the study was not original data, a review article, non-English, at least one of the outcomes of interest were not included, or animal studies.

Variations in the laparoscopic technique in the pancreaticoduodenectomy group included total MIPD and robotic pancreaticoduodenectomy (RPD). Total laparoscopic was defined by completely laparoscopic resection of the head of the pancreas and duodenum, followed by completely intra-corporeal reconstruction of the biliary, pancreatic, and intestinal continuity.

The outcomes of interest were: patient demographics (age, male gender, BMI, malignancy, and tumor size), intraoperative variables (operative time, blood loss, blood transfusions, conversion rate), oncologic variables [number of lymph nodes (LNs), number of patients with positive lymph nodes, and margin positivity], postoperative morbidity and mortality (overall morbidity, 30 day or in-hospital mortality, pancreatic fistula, delayed gastric emptying (DGE), bile leak, bleeding, and wound infections), and post-operative outcomes (length of hospital stay, readmission rates, reoperation rates, time to return of bowel function, time to oral intake, time to ambulation, analgesic requirements, and total hospital cost).

Odds ratios (ORs) were calculated from dichotomous data and the mean difference (MD) from the continuous data, both with 95% confidence intervals (CI). An OR less than 1 represented a more favorable outcome with laparoscopic surgery. Reported medians and ranges were used to estimate means and standard deviations using the method proposed by Hozo *et al.* (14). Heterogeneity was determined among the trials using the Cochrane Q-test (n-1 degree of freedom; $P<0.05$ to denote statistical significance). I^2 was calculated to measure the proportion of total variation in the estimates of treatment effect attributable to heterogeneity beyond chance. If heterogeneity was detected (Q-test, $P<0.10$, or $I^2>50\%$), a random-effects model was applied. Otherwise, a fixed-effects model was used. Meta-regression was used to estimate the extent to which measured covariates (year of study, sample size, ASA of ≥3, malignancy, and tumor size) could explain the observed heterogeneity in the outcomes. Statistical analysis was performed using OpenMeta[Analyst](15).

Results

Laparoscopic distal pancreatectomy (LDP)

Selected studies

A total of 495 articles were reviewed and this analysis pooled data from 42 studies published between 2006 and 2015, which included 18,587 patients. In total, 3,759 were allocated to the LDP group and 14,828 to the open distal pancreatectomy group. No prospective randomized controlled trials were identified.

Patient selection

The mean age of the patients in the LDP group was 54.9±10.8 and 58.4±5.3 years in the open pancreaticoduodenectomy (OPD) group. In the LDP group, 40.0% (n=1,353) of patients were males and 44.1% (n=6,035) in the ODP group. In the LDP group, 40.4% (n=310) of patients had an ASA of ≥3 and 68.2% (n=524) in the OPD group. The indication for operation was malignancy in 27.8% (n=914), benign/premalignant cystic disease in 14.1% (n=464), benign conditions in 43.5% (n=1,432), and neuroendocrine tumors (NETs) in 14.7% (n=483) in the LDP group and malignancy in 34.8% (n=5,031), benign/premalignant cystic disease in 4.5% (n=647), benign conditions in 55.0% (n=794), and NET in 5.7% (n=821) in the ODP group. The mean tumor size in the LDP group was 3.59±0.83 and 4.6±1.3 cm. The contraindications for minimally invasive distal pancreatectomy were rarely reported, but included patient (16-19) and surgeon preference (16,20-23), malignancy (24), and contraindications to laparoscopy (19) (see *Tables 1*,*2*).

Intra-operative considerations

The mean operative time was 231±62.8 minutes in the LDP group versus 216.5±55.0 minutes in the ODP group. Operating room time was longer in the LDP group in 8 studies (25-32), shorter in 4 studies (33-36), and similar in 18 studies (16,18,19,21-23,37-48). Overall, the analysis showed that operating room time was statistically significantly longer in the LDP group (MD 21.169; 95% CI, 11.043 to 21.296) (*Figure 1*). There was a high level of heterogeneity (I^2=82.7%) across studies and subsequent meta-regression analysis indicated that ASA of ≥3 (P=0.034) might be a significant explanation for some of the heterogeneity. The mean estimated blood loss was 276±102.8 cc in the LDP group and 580±280.7 cc in the ODP group. Estimated blood loss (MD –274.553; 95% CI, –351.646 to -197.460) (*Figure 2*) (16,18,21,23,25,26,29-32,34,37,38,42,44,46-48) and the number of red blood cell transfusions (OR 0.562; 95% CI, 0.416 to 0.760, fixed-effects) (*Figure 3*) (16,18,22,26,29-31,35,38,40-42,44,47,49) were statistically significantly lower in the LDP group. The spleen was preserved in 29.9% of patients in the LDP group and 14.4%

Table 1 Patient demographics in the LDP and ODP groups

Studies	Age (years)		Male gender		BMI (kg/m^2)		ASA class	
	LDP	ODP	LDP	ODP	LDP	ODP	LDP	ODP
Teh 2007	53.4	51.5	4 (33%)*	12 (75%)*	26.4	27.5	1. 1 (8%) 2. 10 (84%) 3. 1 (8%)	1. 2 (13%) 2. 10 (62%) 3. 4 (25%)
Eom 2008	46.7±16.7	47.5±14.9	NS	NS	22.2±2.2	23.0±3.4	NR	NR
Kooby 2008	59.0±13.0	58.4±14.3	56 (35.3%)	207 (40.7%)	27.7±6.3	27.0±6.4	2.4±0.7	2.4±0.7
Matsumoto 2008	58.6±17.6	63.2±13.2	7 (50%)	7 (36.8%)	NR	NR	1.3±0.5	1.3±0.4
Nakamura 2009	53.5±18.6	61.5±20.6	6 (30%)	8 (50%)	23.4±2.9	21.3±4.2	1.8±0.6	1.9±0.7
Baker 2009	59.2±3.2	59.3±1.6	9 (33.3%)	39 (45.9%)	NR	NR	NR	NR
Finan 2009	60.5±59	55.5±63	13 (29.6%)	42 (40.4%)	28.3±36.2	26.9±31.2	NR	NR
Aly 2010	47±16	52±16	14 (35%)*	24 (68.6%)*	21±3	21±3	NR	NR
DiNorcia 2010	58.2±14.1	60.2±15.2	22 (31.0%)	73 (38.0%)	NR	NR	NR	NR
Jayaraman 2010	60	64	44 (41.1%)	137 (58%)	27	27	NR	NR
Kooby 2010	65.1±12.3	65.5±11.3	12 (52.2%)	80 (42.3%)	28.5±5.7	26.2±6.0	2.7±0.7	2.6±0.7
Casadeo 2010	59±16.2	62±14.6	4 (18.2%)	4 (18.2%)	NR	NR	1–2. 18 (81.8%) 3–4. 4 (18.2%)	1–2. 18 (81.8%) 3–4. 4 (18.2%)
Vijan 2010	59.0±17.3	58.6±15.2	40 (40%)	50 (50%)	27.4±5.2	27.9±5.0	≥3. 58 (58%)	≥3. 52 (52%)
Butturini 2011	48	53	8 (18.6%)	20 (27.4%)	NR	NR	NR	NR
Baker 2011	57.7±2.9	60.9±1.47	3 (15%)*	25 (50%)*	NR	NR	NR	NR
Cho 2011	174 (69%) <65	306 (70%) <65	87 (34%)*	191 (44%)*	124 (49%)– <27	236 (55%)– <27	1–2. 130 (51%) >2. 123 (49%)	1–2. 201 (46) >2. 233 (54)
Fox 2012	55.3±16.4	58.4±14.4	13 (31%)*	39 (51.3%)*	27.3 [24–31]	26.5 (23.7–29.5)	ASA > 2 22 (52.4)	ASA > 2 40 (52.6)
Limongelli 2012	62.1±6.9	64.1±5.8	6 (37.5%)	23 (79.3%)	26.4±2.5	27.1±2.1	2.3±0.6	2.4±0.5
Abu Hilal 2012	60 [17–78]	63 [18–79]	9 (56.3%)	17 (48.6%)	NR	NR	NR	NR
Mehta 2012	52.4±17.2	59.0±12.8	2.3:1 (F:M)*	1:1 (F:M)*	NR	NR	NR	NR
Soh 2012	58 [42–79]	62 [37–77]	2 (20%)*	13 (61.9%)*	25.0 [21–32]	21.0 (18.7–28.7)	1. 1 (10%) 2. 5 (50%) 3. 4 (40%) 4. 0 (0%)	1. 0 (0%) 2. 15 (71%) 3. 6 (28%) 4. 0 (0%)
Stauffer 2012	65 [17–89]	64 [28–85]	33 (40%)	35 (39%)	26.8 [17–50]	27.7 (17.2–62.5)	2. 22 (27%) 3. 59 (72%) 4. 1 (1%)	2. 19 (21%) 3. 65 (72%) 4. 6 (7%)
Sherwinter 2012	66 [40–86]	62 [40–84]	NR	NR	NR	NR	1. 2 (13%) 2. 5 (31%) 3. 4 (25%) 4. 5 (31%)	1. 2 (18%) 2. 4 (36%) 3. 4 (36%) 4. 1 (9%)
Zhang 2013	35.4±13.0	35.2±16.6	0 (0.0%)	4 (30.8%)	20.8±2.3	22.4±6.1	1. 9 (60%) 2. 6 (40%)	1. 8 (61.5%) 2. 5 (38.5%)

Table 1 (*continued*)

Table 1 (*continued*)

Studies	Age (years)		Male gender		BMI (kg/m^2)		ASA class	
	LDP	ODP	LDP	ODP	LDP	ODP	LDP	ODP
Durlik 2013	59 [24–84]	55 [29–85]	6 (15.4%)*	39 (57.4%)*	NR	NR	NR	NR
Magge 2013	67±2.2	66±2.0	9 (32.1%)	13 (38.2%)	26.7±1.3	26.5±0.7	Median 3 (IQR 3–3)	Median 3 (IQR 2–3)
Zhang 2014	43±11.6	47±13.5	8 (40%)	9 (39.1%)	23.8±2.5	22.7±3.3	1.5±1	1.5±1
Chung 2014	38.2±13.9	49.3±17.0	9 (22.0%)	6 (31.6%)	23.0±3.6	22.3±4.8	NR	NR
Hu 2014	53.1±13.2	49.1±9.5	7 (63.6%)	13 (68.4%)	23.9±4.2	25.6±4.0	NR	NR
Tran 2014	60.7±0.8	58.3±0.2	152 (39.8%)	3,696 (43.1%)	NR	NR	NR	NR
Rutz 2014	58.6±13.5	56.3±16.1	24 (34%)	21 (47%)	27.9±7.0	27.7±5.9	2.57±0.63	2.69±0.51
Braga 2015	61.4±13.5	61.0±13.8	44 (44%)	44 (44%)	NS	NS	1–2. 83 (83%) 3–4. 17 (17%)	1–2. 88 (88%) 3–4. 12 (12%)
Khaled 2015	57 [34–78]	60 [32–78]	8 (36.6%)	8 (36.6%)	26.5 [21–70]	28.3 (24–36.6)	Median 2	Median 2
Lee 2015	58±15.0*	63±13.5*	57 (3.5%)	286 (44.9%)	28.2	28.4	Median 3	Median 3
Nakamura 2015	58±16	59±15	269 (36.9%)	294 (40.3%)	22.4±3.7	22.2±3.7	NR	NR
Rooij 2015	56±13	56±12	33 (52%)	33 (52%)	26±4	25±4	1. 18 (28%) 2. 39 (61%) 3. 6 (9%) 4. 1 (2%)	1. 123 (22%) 2. 361 (63%) 3. 82 (14%) 4. 3 (1%)
Sharpe 2015	67.7±10.1*	65.6±10.5*	NR	NR	NR	NR	NR	NR
Shin 2015	62 [39–86]	64 [45–81]	31 (60.8%)	31 (60.8%)	24.1 [17–30]	23.4 (19.5–28.5)	1. 30 (42.9%) 2. 35 (50%) 3. 5 (7.1%) 4. 0 (0)	1. 31 (38.8%) 2. 37 (46.3%) 3. 11 (13.7%) 4. 1 (1.2%)
Xourafas 2015	61 [20–95]	62 [34–92]	41 (56%)	48 (49%)	27.8	28.4	NR	NR
Yan 2015	50.5±15.1	50.1±14.3	15 (33.3%)	18 (39.1%)	22.1±2.9	21.6±1.6	NR	NR
Adam 2015	64±13	63±14	276 (52%)	575 (48%)	NR	NR	NR	NR
Ricci 2015	58 [15–82]	67 [25–82]	14 (34.1%)	21 (52.5%)	25.3 [18–40]	26.6 (17.0–45.0)	NR	NR

*, statistical significance P<0.05. Data reported as mean ± SD; median (range); n (%). LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy; NR, not recorded.

in the ODP group, which reached statistical significance (OR 0.327; 95% CI, 0.285 to 0.376) (*Figure 4*) (16,17,19-22,24,25,27-29,31-33,36,38,39,42,43,45,48,50,51). There was a high level of heterogeneity among studies evaluating blood loss (I^2=93.3%) and splenic preservation (I^2=90.3%). Meta-regression analysis indicated that malignancy (P<0.001) and tumor size (P=0.029) might be a significant explanation for some of the heterogeneity in the outcome splenic preservation; however, no covariates were able to explain the heterogeneity in blood loss. Conversion rate was reported in 26 articles (n=1,814, 60.5%). LDP was converted to an open procedure in 17.6% of cases (n=320), most commonly due to bleeding (n=51, 15.9%), adhesions (n=19, 5.9%), vessel involvement (n=18, 5.6%), and lack of progress (n=15, 4.7%) (17,18,21,25-27,29,30,33-36,38,39,41-44,48,51-55).

Oncologic outcomes

The mean number of LNs retrieved was 11±4.5 in the LDP group versus 12.8±3.2 in the ODP group, which did

Table 2 Patient surgical indications in the LDP and ODP groups

Studies (TMIPD)	Cases		Tumor size		Surgical indication		Contraindication to MIPD
	LDP	ODP	LDP	ODP	LDP	ODP	
Teh 2007	12	16	3.4	3.4	Malignant 0 Cystic 5 Benign 2 NET 9	Malignant 0 Cystic 5 Benign 2 NET 9	NR
Eom 2008	31	62	3.95±2.3*	6.15±4.1*	Malignant 0 Cystic 18 Benign 11 NET 2	Malignant 0 Cystic 36 Benign 22 NET 4	NR
Kooby 2008	159	508	3.2±1.7	3.3±1.7	Malignant 57 Benign 102	Malignant 247 Benign 261	NR
Matsumoto 2008	14	19	3.0±2.7	3.4±1.7	Malignant 0 Cystic 10 Benign 0 NET 4	Malignant 0 Cystic 18 Benign 0 NET 1	NR
Nakamura 2009	20	16	4.8±3.3	4.1±2.1	Malignant 3 Cystic 10 Benign 3 NET 4	Malignant 1 Cystic 8 Benign 4 NET 2	NR
Baker 2009	27	85	3.78±0.40	4.03±0.39	Malignant 8 Benign 19	Malignant 25 Benign 60	NR
Finan 2009	44	104	3.26±1.20*	7.73±5.48*	Malignant 6 Cystic 24 Benign 5 NET 9	Malignant 37 Cystic 33 Benign 21 NET 13	NR
Aly 2010	40	35	–	–	Malignant 0 Cystic 16 Benign 15 NET 9	Malignant 0 Cystic 17 Benign 16 NET 2	NR
DiNorcia 2010	71	192	2.5 (1.5–4.0)*	3.6 (2.0–6.0)*	Malignant 4 Cystic 36 Benign 6 NET 25	Malignant 65 Cystic 43 Benign 18 NET 31	NR
Jayaraman 2010	107	236	3	3	NR	NR	NR
Kooby 2010	23	189	3.5±1.3	4.5±2.8	Malignant 23	Malignant 189	Surgeon preference
Casadeo 2010	22	22	2.0±3.3*	5.0±4.2*	Malignant 2 Cystic 12 NET 8	Malignant 2 Cystic 12 NET 8	NR
Vijan 2010	100	100	4.0±2.9*	3.3±1.9*	Malignant 23 Cystic 49 Benign 28	Malignant 23 Cystic 43 Benign 34	NR
Butturini 2011	43	73	3.9	4	Malignant 1 Cystic 31 Benign 1 NET 6	Malignant 2 Cystic 41 Benign 6 NET 16	Malignant pathology
Baker 2011	20	50	2.78±0.23	4.01±0.34	Malignant 1 Benign 19	Malignant 20 Benign 30	NR
Cho 2011	254	439	145 (60%)–<3.5*	166 (42%)–<3.5*	Malignant 25 Benign 230	Malignant 127 Benign 312	Surgeon preference

Table 2 (*continued*)

Table 2 (*continued*)

Studies (TMIPD)	Cases		Tumor size		Surgical indication		Contraindication to MIPD
	LDP	ODP	LDP	ODP	LDP	ODP	
Fox 2012	42	76	2.9 (1.5–4.6)	3.5 [2.5–5.8]	Malignant 2 Cystic 17 Benign 9 NET 14	Malignant 2 Cystic 47 Benign 12 NET 15	NR
Limongelli 2012	16	29	3.2±0.6	4.3±1.7	Malignant 5 Cystic 3 Benign 2 NET 6	Malignant 14 Cystic 8 Benign 3 NET 4	NR
Abu Hilal 2012	35	16	3.4 (0.10–10)	3.3 [1.2–9.0]	Malignant 4 Cystic 17 Benign 10 NET 4	Malignant 4 Cystic 1 Benign 8 NET 3	Surgeon preference Patient preference
Mehta 2012	30	30	3.8±2.3	4.3±2.3	Malignant 7 Cystic 8 Benign 3 NET 12	Malignant 7 Cystic 8 Benign 3 NET 12	NR
Soh 2012	10	21	2.45 (0.2–6.7)*	5.0 [1.4–17.0]*	Malignant 3 Cystic 5 Benign 1 NET 3	Malignant 10 Cystic 4 Benign 5 NET 2	NR
Stauffer 2012	82	90	2 [0.5–7.5]	2.8 [0.5–15]	Malignant 18 Cystic 32 Benign 19 NET 13	Malignant 21 Cystic 33 Benign 23 NET 13	NR
Sherwinter 2012	16	11	2.79	3.12	Malignant 4 Cystic 10 Benign 2 NET 2	Malignant 4 Cystic 4 Benign 2 NET 1	NR
Zhang 2013	15	13	5.1±1.6*	7.7±4.1*	Benign 15	Benign 13	Surgeon preference
Durlik 2013	39	68	2.13 (0.12–6.5)*	3.35 [1–9]*	Malignant 6 Cystic 21 Benign 6 NET 6	Malignant 21 Cystic 14 Benign 27 NET 7	Patient preference Tumor within parenchyma
Magge 2013	28	34	3.7 [2.8–4.5]	4.5 [2.8–5.4]	Malignant 28	Malignant 34	NR
Zhang 2014	20	23	5.4±2.3	6.8±3.5	Malignant 4 Cystic 9 Benign 7 NET 0	Malignant 7 Cystic 12 Benign 4 NET 0	Surgeon preference
Chung 2014	41	19	40.8±31.9	53.5±30.6	Malignant 0 Cystic 33 Benign 6 NET 2	Malignant 0 Cystic 14 Benign 3 NET 2	NR
Hu 2014	11	23	2.8±1.5	3.1±1.7	Malignant 11	Malignant 23	Choice of patient
Tran 2014	382	8575	NR	NR	Malignant 139 Benign 242	Malignant 2,418 Benign 6157	NR
Rutz 2014	70	45	3.73±2.82	4.71±4.63	Malignant 11 Cystic 30 Benign 11 NET 18	Malignant 8 Cystic 11 Benign 15 NET 11	NR

Table 2 (*continued*)

Table 2 (*continued*)

Studies (TMIPD)	Cases		Tumor size		Surgical indication		Contraindication to MIPD
	LDP	ODP	LDP	ODP	LDP	ODP	
Braga 2015	100	100	NR	NR	Malignant 33 Cystic 31 Benign 8 NET 28	Malignant 39 Cystic 21 Benign 11 NET 29	NR
Khaled 2015	22	22	NR	NR	Malignant 4 Cystic 4 Benign 5 NET 9	Malignant 5 Cystic 7 Benign 2 NET 8	NR
Lee 2015	131	637	2.5 (1.6–3.8)*	3.5 [2.1–5.0]*	Malignant 19 Cystic 34 Benign 37 NET 41	Malignant 249 Cystic 68 Benign 177 NET 143	NR
Nakamura 2015	729	729	3.5±2.6	3.5±2.8	Benign 729	Benign 729	NR
Rooij 2015	63	63	NR	NR	Malignant 8 Cystic 12 Benign 20 NET 24	Malignant 150 Cystic 155 Benign 148 NET 110	NR
Sharpe 2015	145	625	3.7±1.9*	4.2±3.2*	Malignant 145	Malignant 625	NR
Shin 2015	51	51	3.1 (0.4–8.5)	3.0 [0.5–8.0]	Malignant 51	Malignant 51	No absolute indications
Xourafas 2015	73	98	2.2 (0.2–13)	2.7 [0.4–15]	NET 73	NET 98	NR
Yan 2015	45	46	4.7±3.2	4.5±1.8	Malignant 0 Cystic 28 Benign 8 NET 9	Malignant 0 Cystic 25 Benign 9 NET 12	NR
Adam 2015	535	1198	3.6±2.2*	4.3±4.1*	Malignant 267 Benign 31 NET 221	Malignant 708 Benign 82 NET 375	NR
Ricci 2015	41	40	2.5 (0.5–15)	3 [8–15]	Malignant 18 Benign 23	Malignant 22 Benign 18	Contraindication to laparoscopy Patient refusal

*, statistical significance P<0.05. Data reported as mean ± SD; median (range); n (%). LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy; TMIPD, total minimally invasive pancreaticoduodenectomy; MIPD, minimally invasive pancreaticoduodenectomy; NR, not recorded.

not reach statistical significance (MD −1.636; 95% CI, −4.893 to 1.622) (18,21,23,26,35,37,39,43,45,47,48,52,56). The number of patients with positive LNs in the LDP group was 29.6% versus 36.8% in the ODP group and was not significant (OR 0.951; 95% CI, 0.710 to 1.273, fixed-effect model) (18,23,33,44,51,56) in the LDP versus ODP group. There was a high level of heterogeneity among studies evaluating the total number of LNs (I^2=97.4%) and no covariate on meta-regression analysis explained the heterogeneity significantly; however, there was a trend with malignancy (P=0.066). The rate of positive margins was 6.1% in the LDP group and 12.3% in the ODP group. The LDP group had a statistically significant lower positive margin rate than the ODP group (OR 0.569; 95% CI, 0.422 to 0.768, fixed effect model) (*Figure 5*) (16,21,23,26,28,29, 33,43,44,51,56).

Morbidity and mortality

The rate of overall complications was 32.1% in the LDP group and 40.2% in the ODP group. Complication rates were lower in the LDP group in 9 studies (20,31-33,36,43,50,51,53) and no different in the remaining 25 studies (16,17,19,22-31,35,37,39-42,44-49,55). Overall, the analysis showed a significantly lower complication rate

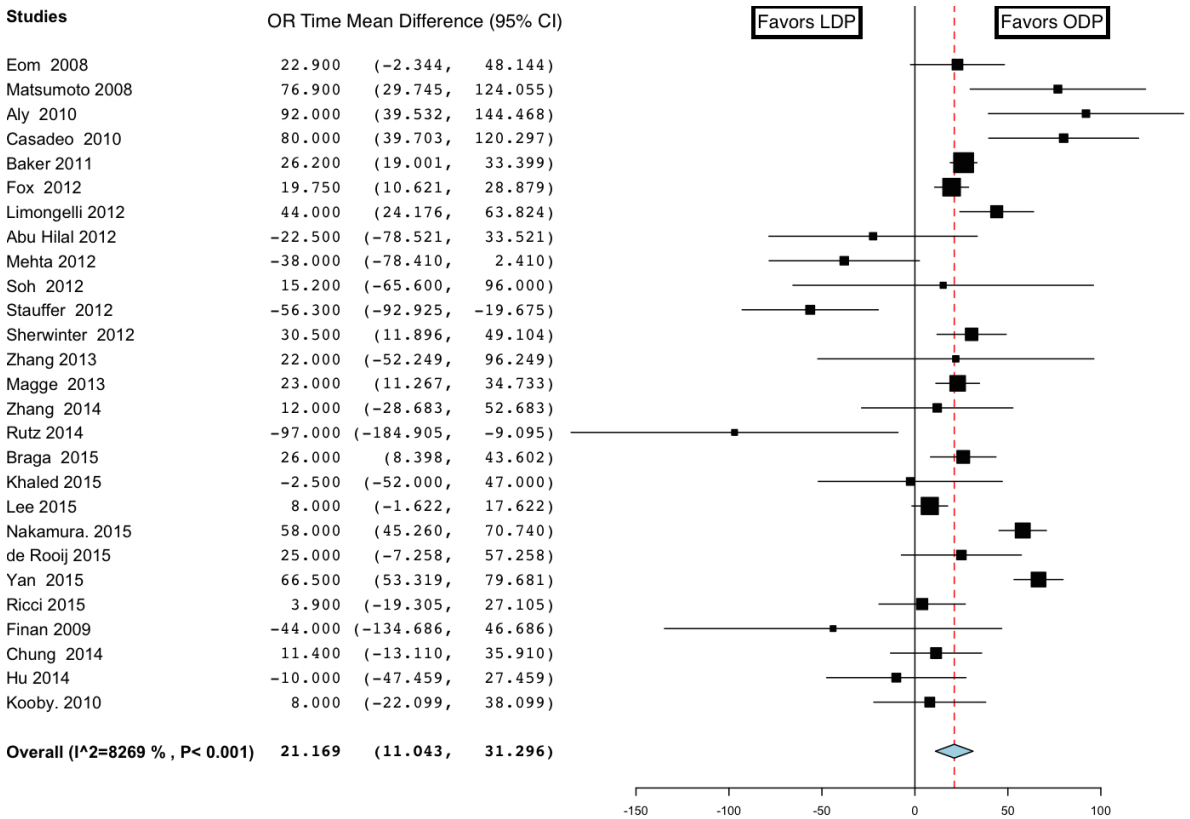

Figure 1 Operating room times in laparoscopic and open distal pancreatectomy. MD, mean difference; OR, odds ratio; CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

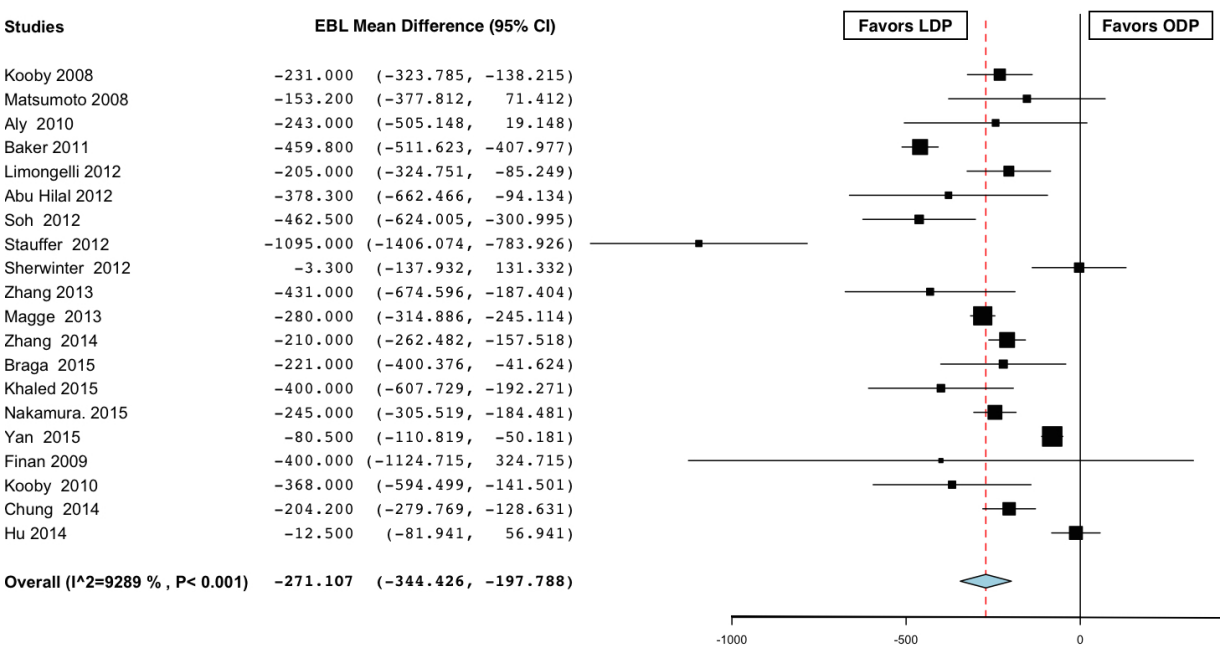

Figure 2 Estimated blood loss in laparoscopic and open distal pancreatectomy. MD, mean difference; CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

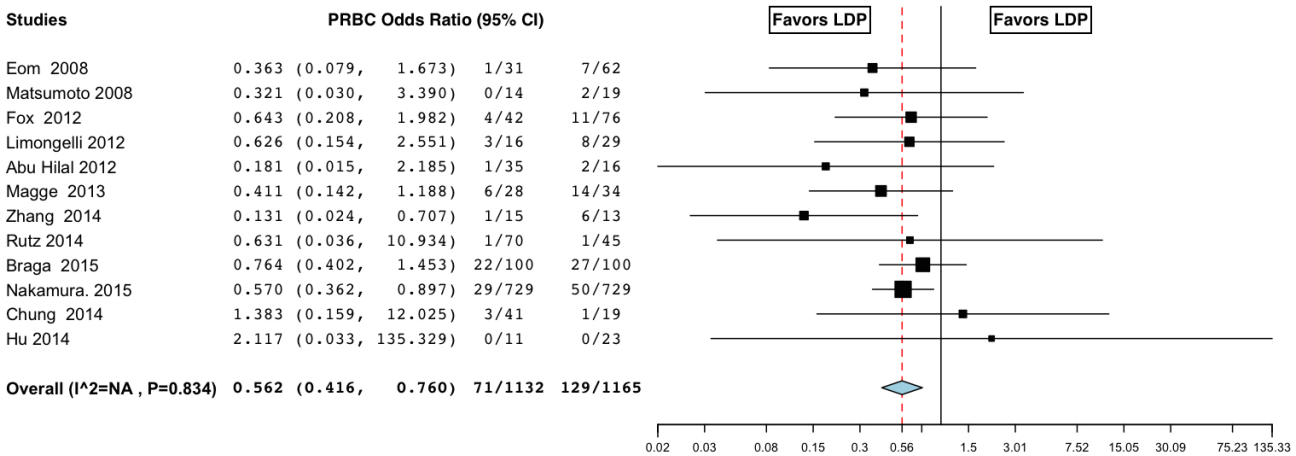

Figure 3 Packed red blood cell transfusion intraoperatively in laparoscopic and open distal pancreatectomy. CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

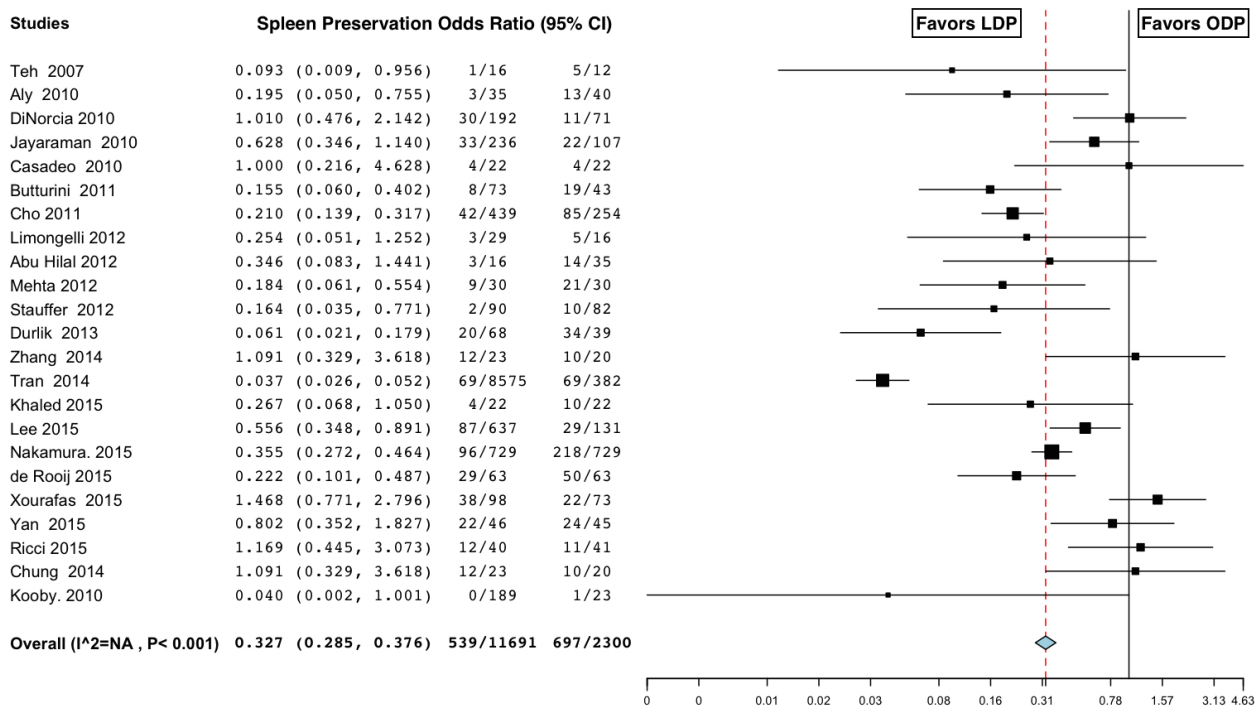

Figure 4 Rate of spleen preservation in laparoscopic and open distal pancreatectomy. OR, odds ratio; CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

in the LDP group (OR 0.699; 95% CI, 0.571 to 0.856, P<0.001, I^2=62.5%) (*Figure 6*). In-hospital or 30-day mortality was 0.6% in the LDP group and 2.6% in the ODP group. Fourteen studies reported zero percent mortality in both groups (18,23-27,30,32,36,38,40,44,46,47). Although not statistically significant, mortality was higher in the LDP group in one study (55) and lower in 14 studies (16,17,20, 21,28,29,31,33,34,37,45,50,51,57). Overall, the analysis showed a significantly lower 30-day mortality or in-hospital mortality in the LDP group (OR 0.562; 95% CI, 0.388 to 0.814, P=0.002, fixed effect model) (*Figure 7*). There was a high level of heterogeneity among studies evaluating

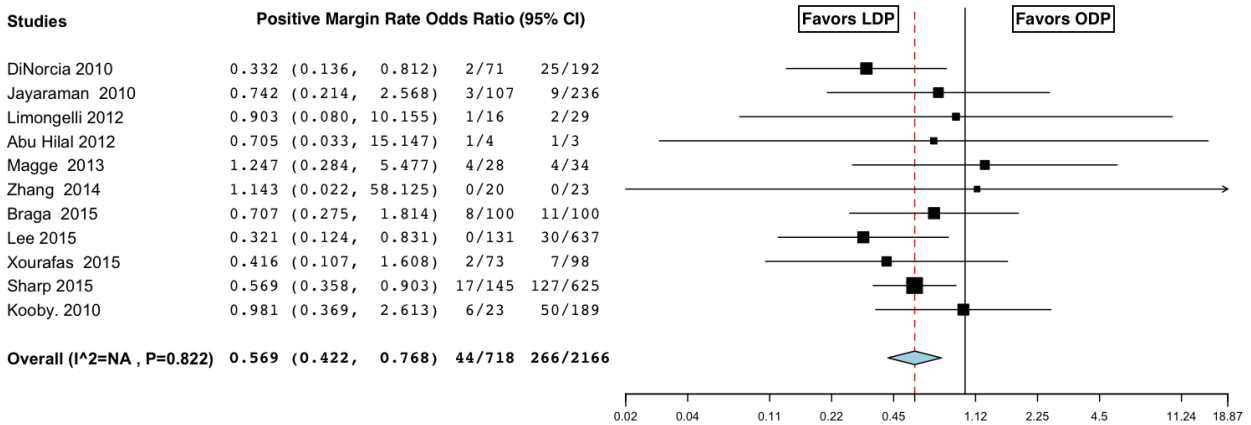

Figure 5 Rate of positive margins in laparoscopic and open distal pancreatectomy. CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

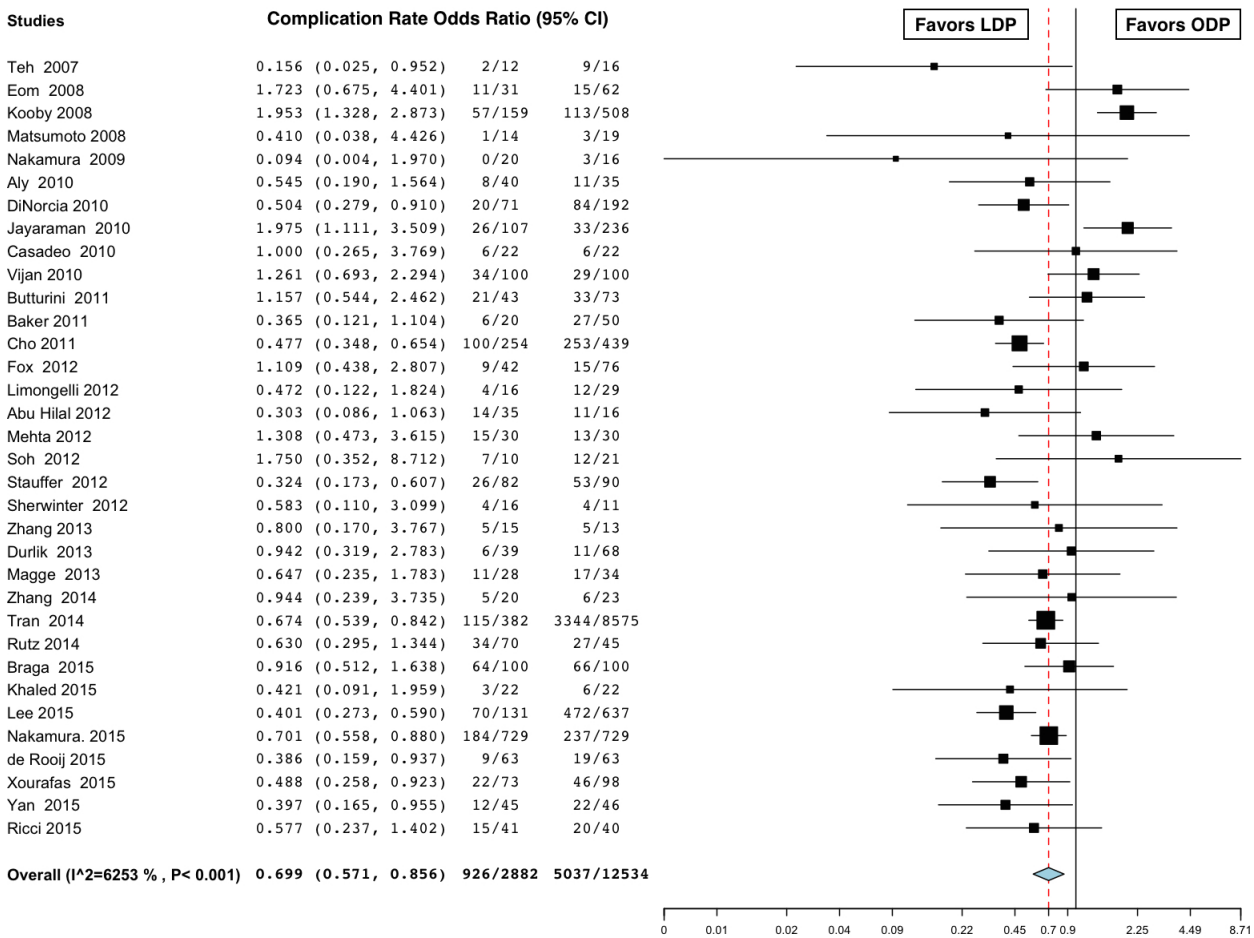

Figure 6 Overall morbidity in laparoscopic and open distal pancreatectomy. CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

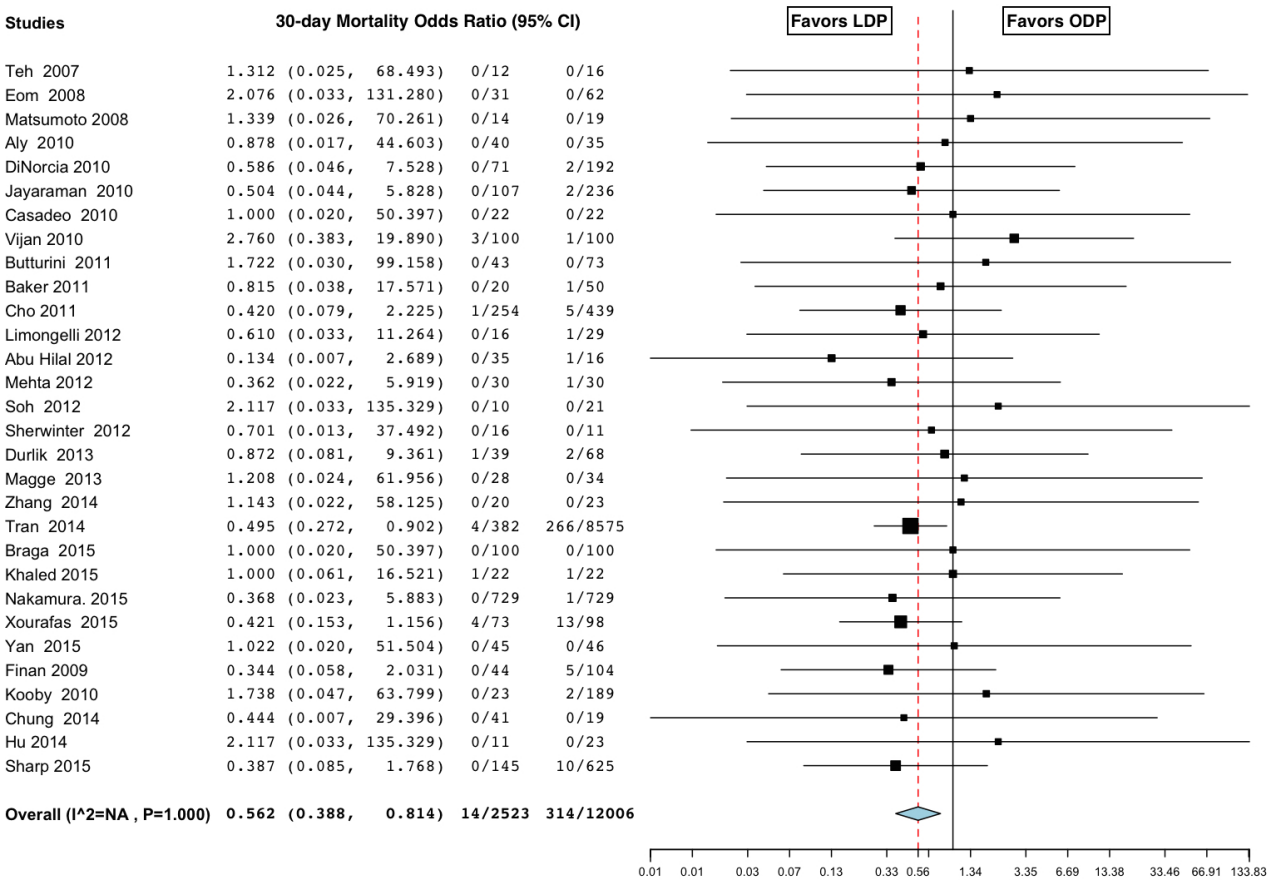

Figure 7 Overall 30-day or in-hospital mortality in laparoscopic and open distal pancreatectomy. CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

overall complication rates (I^2=62.5%) and meta-regression analysis indicated that year of surgery (P=0.001) might be a significant explanation for some of the heterogeneity. Thirty-three percent of patients in the LDP group developed a pancreatic fistula versus 26% in the ODP group and only one study reported a significantly higher pancreatic fistula rate in the LDP group (28.5% versus 13.3%) (41). Although not statistically significant, the rate of pancreatic fistula was lower in the LDP group in 19 studies (16,18,20,22,23,25-27,29,32,33,37,39,43,44,48,49,51,53), higher in 13 studies (17,19,24,28,31,34,36,38,40,42,45,47, 55,58), and equivalent in 2 studies (35,54). Overall, the analysis showed a statistically similar rate of pancreatic fistula in the two groups (OR 1.040; 95% CI, 0.917 to 1.181, P=0.539, fixed effect model). There was no difference in the need for re-operation between the groups (OR 0.823; 95% CI, 0.546 to 1.242, P=0.354, fixed effect model) (18-20,22,24,26,28-30,32,33,36,41,42,44,45,48,51,53). In the LDP group, 5.1% of patients had bleeding post-operatively versus 18.2% in the ODP group; however, this did not reach significance (OR 1.269; 95% CI, 0.546 to 2.948, P=0.579, fixed effect model) (17,19,24,26,29,31,32,39,47, 48,50). Patients in the LDP group had a wound infection rate of 1.9% versus 2.3% in the ODP group, which was significant (OR 0.505; 95% CI, 0.356 to 0.716, fixed effect model) (*Figure 8*) (20,25,26,29,31,32,34,36,39,47,48,50,53,54).

Post-operative outcomes

The length of stay in the LDP group was 9±4.4 days compared to 12±5.0 days in the ODP group and was significant (MD −3.097; 95% CI, −3.722 to −2.474) (*Figure 9*) (16-19,21,23,25-27,29-32,35,37,38,40,44-48,50,51,55). Return of bowel function occurred at a mean of 2.3±0.5 days in the LDP group compared to 3.7±0.5 days (MD −1.355; 95% CI, −2.051 to −0.660) (*Figure 10*) (23,25,26,30,38,49). Patients were able to tolerate oral

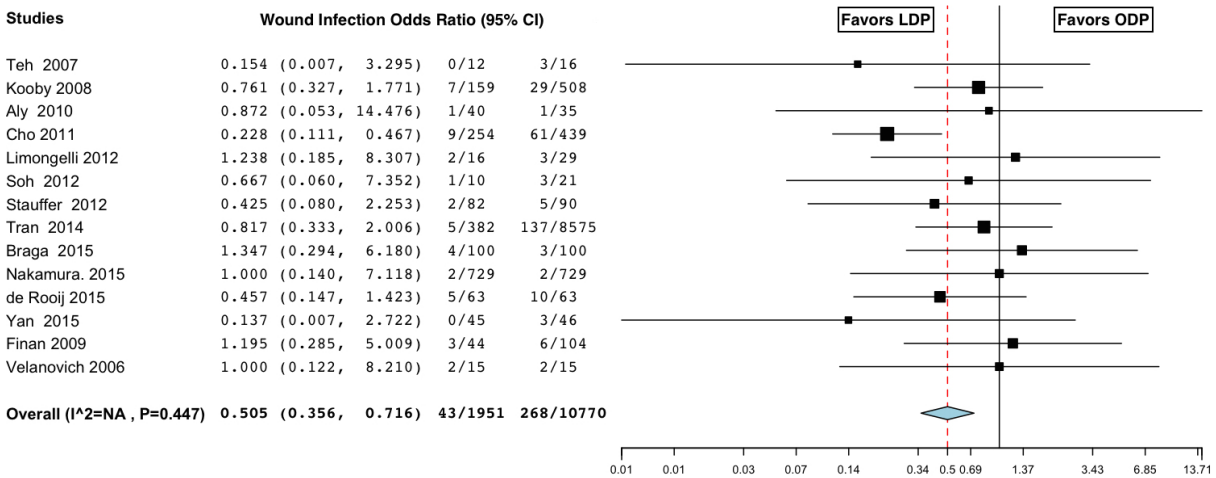

Figure 8 Wound infection rates in laparoscopic and open distal pancreatectomy. CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

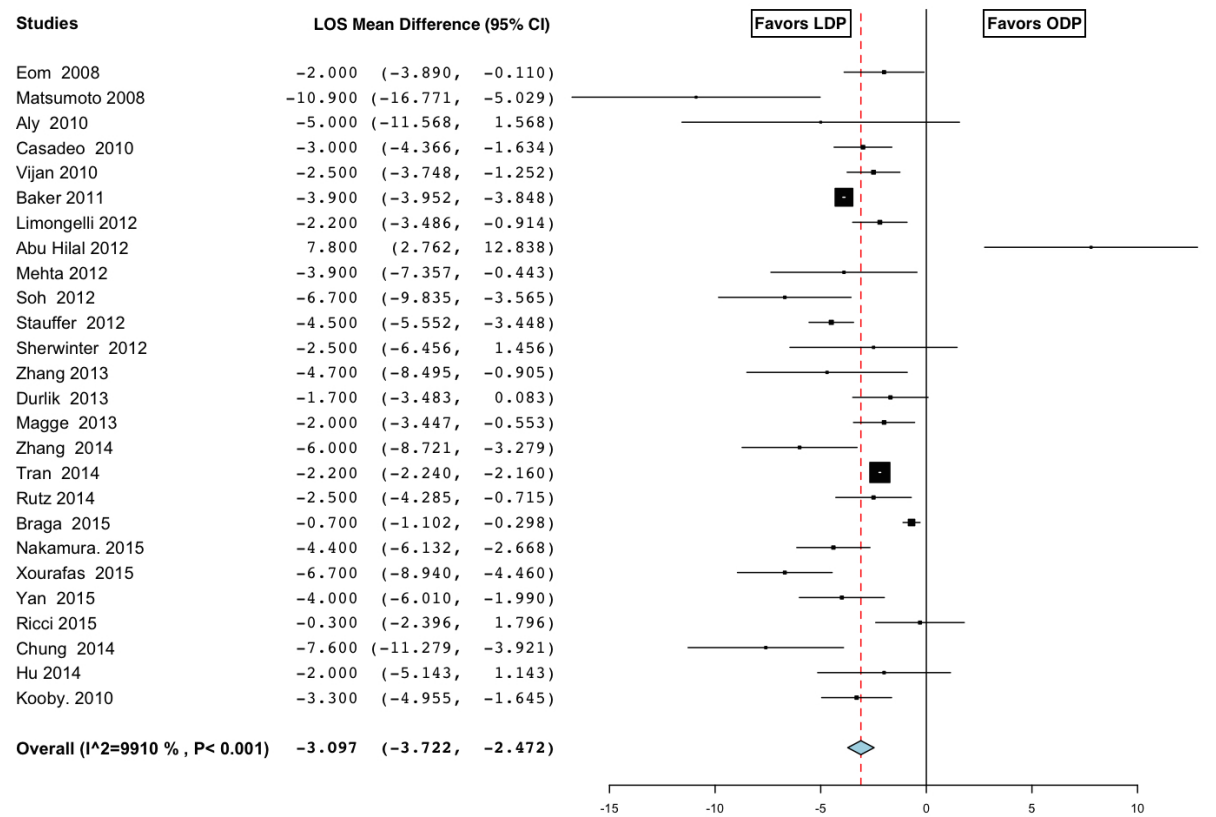

Figure 9 Length of hospital stay in laparoscopic and open distal pancreatectomy. MD, mean difference; CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

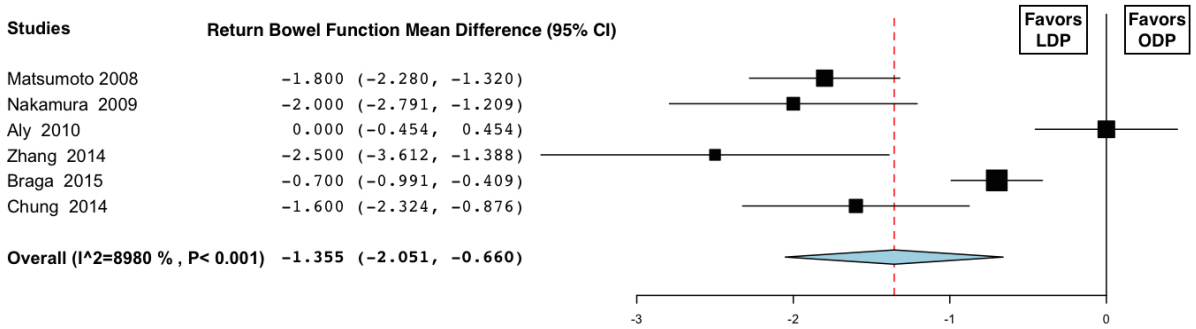

Figure 10 Time to return of bowel function in laparoscopic and open distal pancreatectomy. MD, mean difference; CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

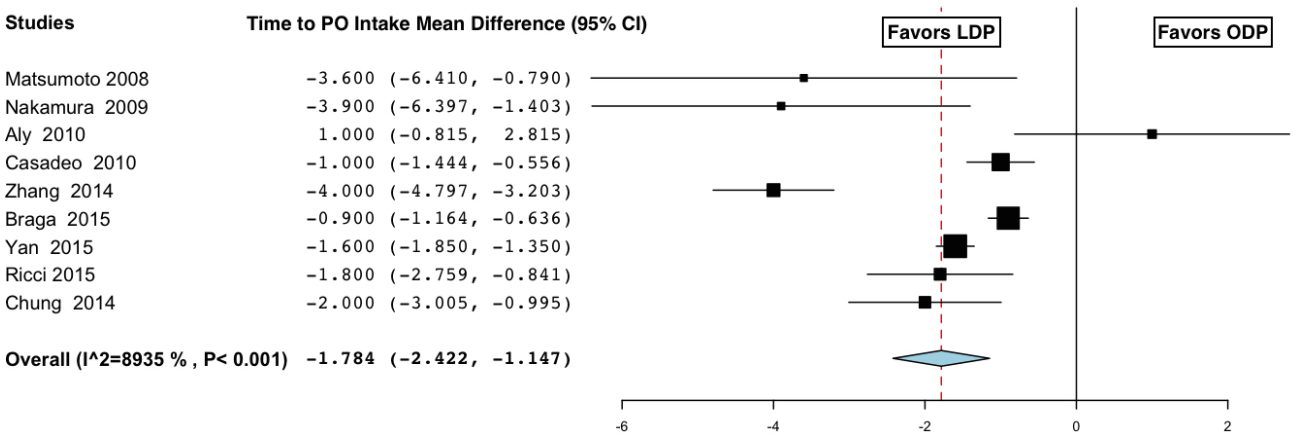

Figure 11 Time to oral intake in laparoscopic and open distal pancreatectomy. MD, mean difference; CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

intake in the LDP group at 3.3±1.7 *vs.* 5.2±1.5 days in the ODP group (MD −1.784; 95% CI, −2.422 to −1.147, I^2=89.3%) (*Figure 11*) (19,23,25-27,30,32,38,49). Similarly, patients in the LDP group required fewer days of IV narcotics (MD −1.565; 95% CI, −2.251 to −0.678, P=0.001, fixed effect model) (*Figure 12*) (25,30,38) compared to the ODP group. There was a high level of heterogeneity among studies evaluating LOS (I^2=99.1%), return of bowel function (I^2=89.3%), and time to PO intake (I^2=89.3%) and meta-regression analysis indicated that ASA of ≥3 (P<0.001) may be a significant explanation for some of the heterogeneity in these studies. The readmission rate in the LDP group was 12.3% versus 8.4% in the ODP group, which did not reach significance (OR 1.051; 95% CI, 0.494 to 2.234, P=0.898, I^2=88.8%) (26,28,29,33-35,37,39,41,44,45,51,52,56). There was no difference in time to ambulation (LDP 1.5±0.5 *vs.* ODP 2.2±1.3) (MD −0.451; 95% CI, −0.958 to 0.056, P value 0.081, I^2=87.2%) (25,30,32). There was a high level of heterogeneity among studies evaluating readmission rates (I^2=88.8%) and time to ambulation (I^2=87.2%). On meta-regression analysis, both age (P=0.008) and sample size (P=0.008) may explain heterogeneity significantly in the studies evaluating time to ambulation, and there was a trend with age (P=0.052) on readmission rates.

Laparoscopic pancreaticoduodenectomy

Selected studies

A total of 495 articles were reviewed, 19 of which were selected and included in the analysis. Fourteen articles were reviewed comparing MIPD to OPD. These articles included 24,457 patients (MIPD/OPD =3,510/20,947). Five articles were reviewed comparing RPD to OPD. The MIPD group included a total of 466 patients (RPD/OPD =182/184). No

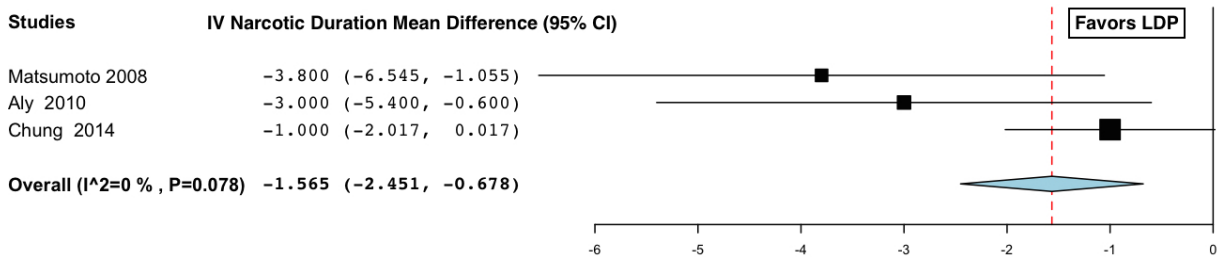

Figure 12 Days of intravenous narcotics in laparoscopic and open distal pancreatectomy. MD, mean difference; CI, confidence interval; LDP, laparoscopic distal pancreatectomy; ODP, open distal pancreatectomy.

prospective randomized controlled trials were identified.

Patient selection

The mean age of patients in the MIPD group was 62.9±6.4 and 61.8±5.7 years in the OPD group. In the MIPD group, 54.0% (n=1,202) of patients were males and 51.4% (n=11,223) in the OPD group. In the MIPD group, 40.2% (n=126) of patients had an ASA of ≥3 and 48.7% (n=252) in the OPD group. The indication for operation was malignancy in 81.2% (n=1,653), benign/premalignant cystic disease in 5.4% (n=110), benign conditions in 6.7% (n=104), and NETs in 6.7% (n=137) in the MIPD group. The indication for operation was malignancy in 89.5% (n=10,035), benign/premalignant cystic disease in 1.2% (n=137), benign conditions in 4.7% (n=529), and NET in 4.6% (n=514) in the OPD group. The mean tumor size in the MIPD group was 2.89±0.56 and 3.08±0.51 cm. The most common contraindications to minimally invasive techniques reported in this review were neoadjuvant chemotherapy (59-62), hostile local conditions secondary to severe pancreatitis or previous complex abdominal operations (60,61,63,64), and need for potential vascular resection (59-61,63-70) (see *Tables 3,4*).

Intra-operative considerations

The mean operative time was MIPD was 470±58.9 minutes in the MIPD group and 375±84.9 minutes in the OPD group, which was significantly longer (MD 96.510; 95% CI, 56.622 to 136.397) (*Figure 13*) (59,63-66,68,69,71-73). There was a high level of heterogeneity (I^2=94.8%) across studies and subsequent meta-regression analysis indicated that factors of tumor size (P<0.001) and ASA ≥3 (P=0.036) might be significant explanations for some of the heterogeneity. The reported estimated blood loss in the MIPD group was 542.4±353 and 911±497.8 cc in the OPD group (MD −351.083; 95% CI, −720.592 to 18.425) (60,63-66,71,72). There was a high level of heterogeneity (I^2=98.7%) across studies and subsequent meta-regression analysis indicated that patient age (P<0.018), malignancy (P<0.001), and year (P=0.002) might be significant explanations for some of the heterogeneity. Despite similar blood loss, patients in the MIPD group required fewer red blood cell transfusions (OR 0.611; 95% CI, 0.422 to 0.884, fixed effect model) (*Figure 14*) (59,60,62,66,67). Conversion to an open operation was reported in 14 articles (59,60,62,63,65-74): 24.3% (n=332) of cases in the MIPD group and 6.0% (n=11) in the RPD group.

Oncologic outcomes

The mean number of LNs retrieved in the MIPD group was 17±4.9 and 16±4.7 LNs in the OPD group. In the analysis, the number of LNs retrieved was equivalent (MD 1.401; 95% CI, −0.468 to 3.271) (56,59,60,62-68,70,71,73,75,76). There was a high level of heterogeneity (I^2=93.7%) across studies and subsequent meta-regression analysis indicated that ASA ≥3 (P<0.001) might explain some of the heterogeneity. Seventy percent of patients in the MIPD group had a positive LN compared to 66.4% in the OPD, which did not reach significance (OR 1.180; 95% CI, 0.969 to 1.435, fixed effect model) (56,67,76). The rate of positive margins was 17.3% in the MIPD group and 23.6% in the OPD group (OR 0.764; 95% CI, 0.607 to 0.962, fixed effect model) (*Figure 15*) (56,65,70,71,76).

Morbidity and mortality

The overall complication rate in the MIPD was 22.5% and 33.6% in the OPD group (OR 1.338; 95% CI, 0.905 to 1.978) (59,60,62-64,66,68,69,71-73,77). In-hospital or 30-day mortality was 3.9% in the MIPD group and 10.3% in the OPD group, which did not reach significance mortality (OR 1.091; 95% CI, 0.433 to 2.751)

Table 3 Patient demographics in the MIPD and OPD groups

Studies	Age (years)		Male gender		BMI (kg/m^2)		ASA	
	MIPD	OPD	MIPD	OPD	MIPD	OPD	MIPD	OPD
TLPD								
Zureikat 2011	69.8±10.2	67.4±11	11 (78.6%)	7 (50%)	28.5 (IQR 4.9)	30.0 (IQR 4.0)	2. 5 (35.7%) 3. 9 (64.3%) 4. 0 (0)	2. 7 (50%) 3. 7 (50%) 4. (0)
Asbun 2012	62.9±14.14	67.3±11.53	29 (54.7%)	95 (44.2%)	27.64±7.16	26.6±5.08	2. 13 (24.5%) 3. 39 (73.6%) 4. 1 (1.9%)	2. 37 (17.2%) 3. 163 (75.8%) 4. 13 (6%)
Mesleh 2013	NR	NR	43 (57%)	23 (48%)	17 (23%) >30	8 (15%) >30	3/4. 60 (80%)	3/4. 44 (92%)
Croome 2014	66.6±9.6	65.4±10.9	51 (47.2%)*	131 (61.2%)*	27.4±5.4	27.2±5.3	NR	NR
Speicher 2014	64 [58–72]	61 [57–69]	36 (42.9%)	9 (36%)	25 [22–29]	24 [24–29]	NR	NR
Hakeem 2014	67.0±10.2	66.3±10.3	8 (66.7%)	8 (66.7%)	25.8±3.7	26.9 ±4.8	1. 5 (41.7%) 2. 7 (58.3%)	1. 4 (33.3%) 2. 8 (66.7%)
Croome 2015	69.5±9.0*	63.6±11.3*	17 (54.8%)	33 (56.9%)	26.1±4.7	26.2±4.8	NR	NR
Dokmak 2015	60 [27–85]	63 [47–81]	26 (57%)	26 (57%)	22.6 [17–30]*	26.4 [19–42]*	NR	NR
Song 2015	49.6±13.4	50.1±13.4	47 (50.5%)	47 (50.5%)	22.8±2.7	23.1±2.5	1.0 (1–2%)	1.0 (1–2%)
Senthilnathan 2015	54±11.6	56±10.8	M:F 1:1.6	M:F 1:1	27.6	28.1	NR	NR
Sharpe 2015	66.1±10.85	65.6±10.4	NS	NS	NR	NR	1. 6 2. 19 3. 5	1. 6 2. 18 3. 6
Adam 2015	66±12	65±11	493 (50%)	3,105 (51%)	NR	NR	NR	NR
Tan 2015	59.3±9.3	59.9±10.4	18 (60%)	23 (76.7%)	NR	NR	NR	NR
Tran 2015	67 [58–73]*	65 [56–73]*	377 (55.4%)	7,701 (51.7%)	NR	NR	NR	NR
Robotic PD								
Buchs 2011	63±14.5*	56±15.8*	22 (50%)	14 (35.9%)	27.7±5.4*	24.8±4.7*	2.5±0.5*	2.15±0.7*
Lai 2012	66.4±11.9	62.1±11.2	12 (60%)	38 (56.7%)	NR	NR	1. 4 (20%) 2. 16 (80%) 3. 0 (0)	1. 5 (7.5%) 2. 62 (92.5%) 3. 0 (0)
Chalikonda 2012	62.6 [51–78]	61 [49–80]	16 (54%)	16 (54%)	24.8	25.6	3. 16 (53%)	3. 23 (76%)
Bao 2014	68.0±11.2	67.7±12.5	13 (46%)	13 (46%)	26 (18.6–39.8)	24 (19.6–41.9)	NR	NR
Chen 2015	53.6±13.5	53.8±14.3	34 (56.7%)	65 (54.2%)	23.2±2.7	22.6±3.4	1. 6 (10%) 2. 53 (88.3%) 3. 1 (1.7%)	1. 10 (8.3%) 2. 108 (90%) 3. 2 (1.6%)

*, statistical significance P<0.05. Data reported as mean ± SD; median (range); n (%). MIPD, minimally invasive pancreaticoduodenectomy; ODP, open distal pancreatectomy; TLPD, total laparoscopic pancreaticoduodenectomy; NR, not recorded.

(56,59,60,62,64-66,68,70-73,75,77). Eight percent of patients in the MIPD group developed pancreatic fistulas compared to 3.1% in the OPD group (OR 0.948; 95% CI, 0.733 to 1.226, fixed effect model) (59,60,62-66,68-73,75). The rate of DGE was 3.4% in the MIPD group and 1.8% in the OPD group (OR 0.744; 95% CI, 0.527 to 1.050, fixed effect model) (59,60,63-69,71,73). The rate of bile leak was 1.0% in the MIPD group and 0.4% in the OPD group (OR 0.834; 95% CI, 0.411 to 1.695, fixed effect model) (59,60,63,66,68,73). Wound infections were similar occurring in 1.7% of patients in the MIPD group and 1.6% in the OPD group (OR 0.642; 95% CI, 0.404 to

Table 4 Patient surgical indications in the MIPD and OPD groups

Studies (TLPD)	Cases		Tumor size		Surgical indication		Contraindication to MIPD
	MIPD	OPD	MIPD	OPD	MIPD	OPD	
Zureikat 2011	14	14	2.2 (0.8–4.7)*	3.6 [3–5]*	Malignant 12 Cystic 1 Benign 1 NET 0	Malignant 11 Cystic 1 Benign 2 NET 0	Risk of positive margin Neoadjuvant chemo
Asbun 2012	983	6,078	2.74±1.6	3.14±1.5	Malignant 34 Cystic 10 Benign 3 NET 6	Malignant 134 Cystic 36 Benign 34 NET 11	Major portal vein resection Hostile abdomen Pancreatitis complications
Mesleh 2013	75	48	NR	NR	Malignant 59 Cystic 14 Benign 2	Malignant 37 Cystic 5 Benign 6	Urgent resection Limited operating room availability Vein resection Patient preference
Croome 2014	108	214	3.3±1.0	3.3±1.3	Malignant 108	Malignant 214	Vein resection
Speicher 2014	25	84	2 [1–4]	3 [2–4]	Malignant 20 Benign 5	Malignant 62 Benign 22	Vein resection Surgeon preference Patient factors
Hakeem 2014	12	12	1.98±10.3	1.92±7.3	Malignant 12	Malignant 12	Pancreatic head tumors
Croome 2015	31	58	3.6±1.1	3.8±1.4	Malignant 25 Cystic 2 Benign 4	Malignant 51 Cystic 3 Benign 4	NR
Dokmak 2015	46	46	2.82 (1.2–4)	2.51 (1.5–4)	Malignant 18 Cystic 6 Benign 16 NET 6	Malignant 19 Cystic 8 Benign 17 NET 5	Vascular resection Neoadjuvant chemoradiotherapy Pancreatitis Suspected diffuse IPMN Division of median arcuate lig.
Song 2015	93	93	2.8±0.6	3.0±1.2	Malignant 5 Cystic 51 Benign 19 NET 18	Malignant 6 Cystic 49 Benign 20 NET 18	Vascular resection Severe pancreatitis Previous major abdominal surgery Combined operation needed
Senthilnathan 2015	45	118	2.8	3.1	NR	NR	Multiple previous surgeries Chronic pancreatitis Neoadjuvant chemoradiotherapy Vascular resection
Sharpe 2015	384	4,037	3.2±1.3	3.3±2.4	Malignant 384	Malignant 4,037	NR
Adam 2015	983	6,078	3.4 ±3.7	3.4±2.8	Malignant 831 Benign 47 NET 105	Malignant 5,234 Benign 370 NET 474	NR
Tan 2015	30	30	NR	NR	Malignant 27 Benign 3	Malignant 26 Benign 4	Malignant pancreatic disease
Tran 2015	681	4,037	NR	NR	NR	NR	NR
Robotic PD							
Buchs 2011	44	39	NR	NR	Malignant 33 Cystic 5 Benign 6	Malignant 27 Cystic 2 Benign 10	Vascular invasion Anesthesia related contraindication

Table 4 (*continued*)

Table 4 (*continued*)

Studies (TLPD)	Cases		Tumor size		Surgical indication		Contraindication to MIPD
	MIPD	OPD	MIPD	OPD	MIPD	OPD	
Lai 2012	20	67	2.1±0.7	2.9±0.7	Malignant 16 Cystic 1 Benign 3 NET 0	Malignant 52 Cystic 4 Benign 8 NET 3	Vascular invasion ASA ≥3
Chalikonda 2012	30	30	2.9 (0.6–6.5)	3 [1–7]	Malignant 14 Cystic 4 Benign 12	Malignant 14 Cystic 4 Benign 12	NR
Bao 2014	28	28	NR	NR	Malignant 17 Cystic 4 Benign 5 NET 2	Malignant 23 Cystic 1 Benign 1 NET 3	Vascular resection
Chen 2015	60	120	2.9±1.4	3.0±1.3	Malignant 38 Cystic 12 Benign 10	Malignant 76 Cystic 24 Benign 20	Tumor >10 cm invading organs Vessel involvement >3 cm Treatment other than whipple Neoadjuvant chemoradiotherapy Anesthesia related contraindication Metastasis

*, statistical significance P<0.05. Data reported as mean ± SD; median (range); n (%).MIPD, minimally invasive pancreaticoduodenectomy; ODP, open distal pancreatectomy; TLPD, total laparoscopic pancreaticoduodenectomy; NR, not recorded.

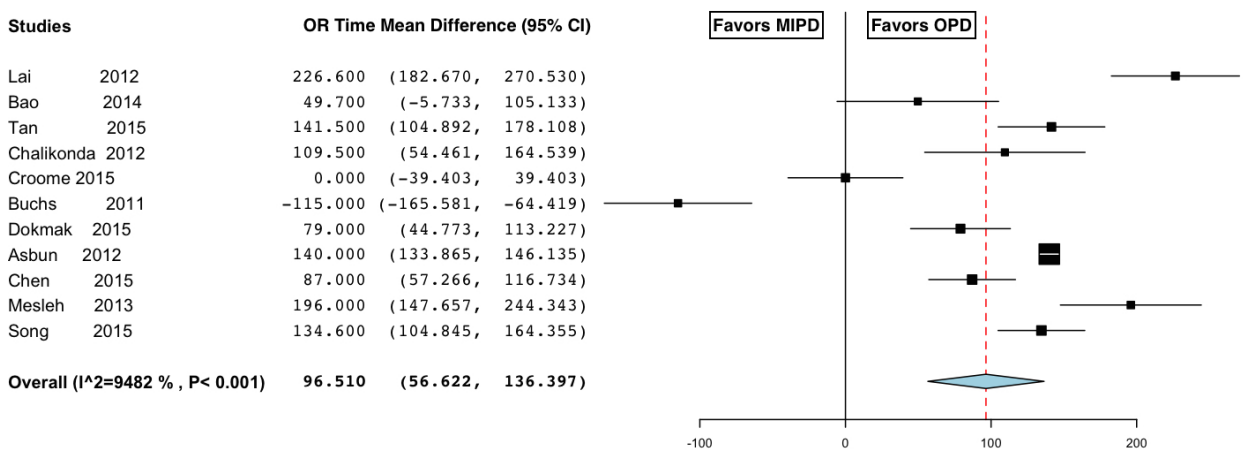

Figure 13 Operating room time in laparoscopic and open pancreaticoduodenectomy. OR, odds ratio; MD, mean difference; CI, confidence interval; MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

1.021, fixed effect model) (59,63,65,66,68,70,71,75). Post-operative bleeding was more common in the MIPD group, 1.9% versus 0.5% (OR 2.028; 95% CI, 1.107 to 3.715, fixed effect model) (*Figure 16*) (59,60,63,66-68,71,73). There was a high level of heterogeneity across studies evaluating overall morbidity (I^2=69.6%) and in-hospital mortality (I^2=76.7%) and subsequent meta-regression analysis indicated that sample size (P=0.004) might explain some of the heterogeneity in mortality; however, no factors were found to be significant for overall morbidity.

Post-operative outcomes

The mean length of stay in the MIPD group was 17±9.7 and 19±8.8 days in the OPD group, which was significantly

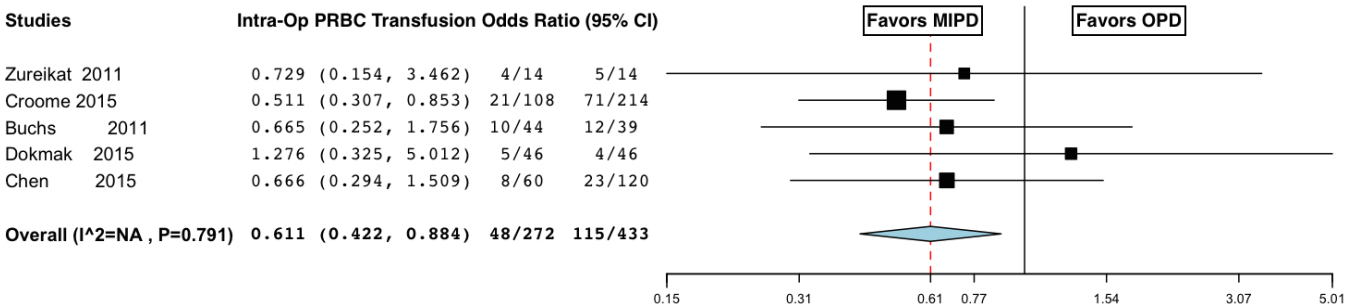

Figure 14 Packed red blood cell transfusions in laparoscopic and open pancreaticoduodenectomy. CI, confidence interval; MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

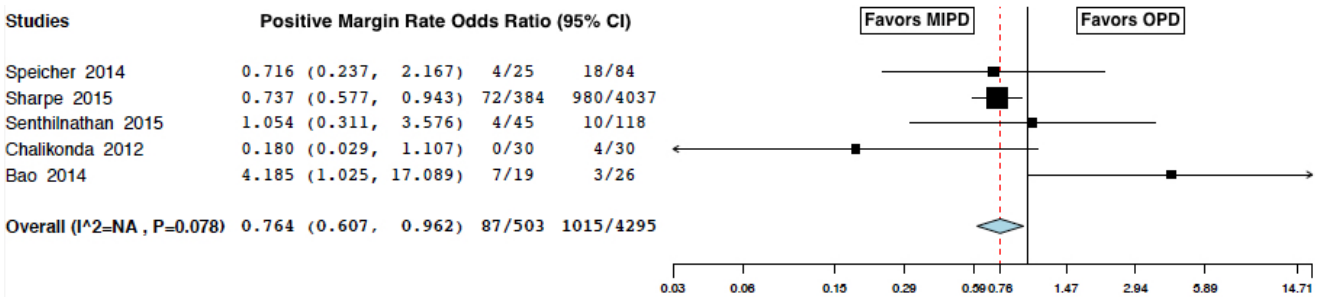

Figure 15 Positive margin rates in laparoscopic and open pancreaticoduodenectomy. CI, confidence interval; MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

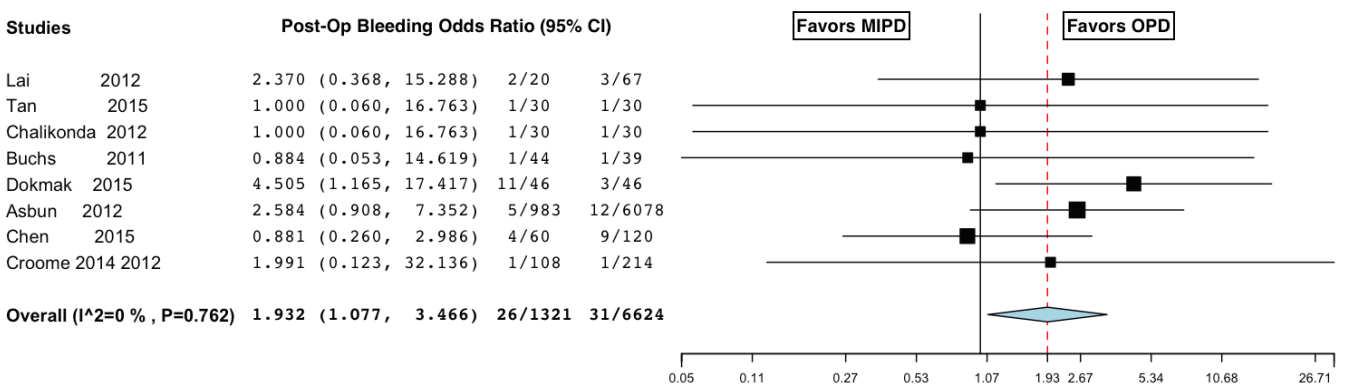

Figure 16 Post-operative bleeding in laparoscopic and open pancreaticoduodenectomy. CI, confidence interval; MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

shorter (MD –2.545; 95% CI, –3.852 to –1.237) (*Figure 17*) (56,59,60,63-66,68,69,72,73,75,77). There was a high level of heterogeneity across studies (I^2=95.2%) and subsequent meta-regression analysis indicated that tumor size (P<0.001) and age (P<0.001) might explain some of the heterogeneity. Bowel function returned on average at 2.8±1.1 days in the MIPD group *vs.* 3.7±1.7 days in the OPD group, which was significantly quicker (MD –1.757; 95% CI, –2.025 to –1.488, fixed effect model) (*Figure 18*) (59,73). Similarly, patients in the MIPD group started PO intake at 4±1.3 days compared to 5.3±0.8 days in the OPD group (MD –1.423; 95% CI, –1.923 to –0.923), fixed

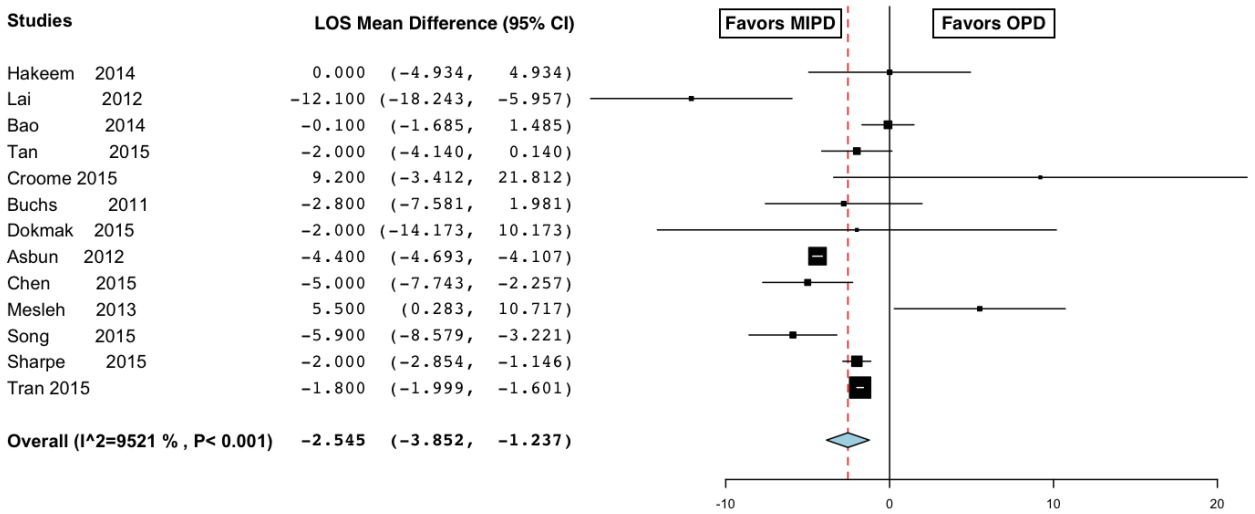

Figure 17 Length of hospital stay in laparoscopic and open pancreaticoduodenectomy. CI, confidence interval; MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

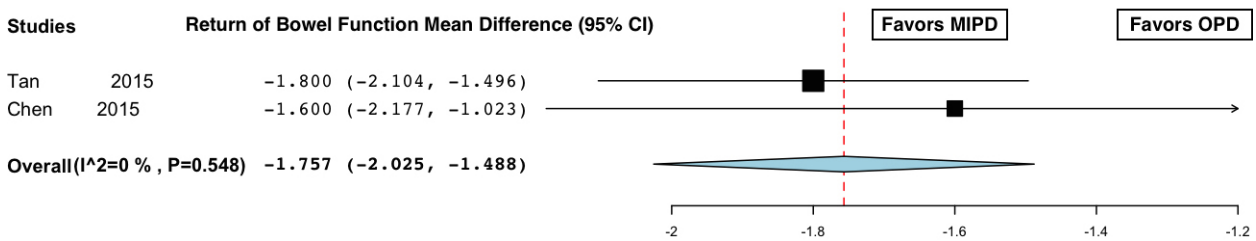

Figure 18 Time to return of bowel function in laparoscopic and open pancreaticoduodenectomy. MD, mean difference; CI, confidence interval; MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

effect model) (*Figure 19*) (59,64) than the open group. Patients in the MIPD group had similar reoperation rates (MIPD 2.3% *vs*. OPD 0.8%) (OR 0.958; 95% CI, 0.587 to 1.564, fixed effect model) (59,60,62,63,65,66,68-71) and readmission rates (MIPD 7.2% *vs*. OPD 9.1%) (OR 0.710; 95% CI, 0.497 to 1.014, fixed effect model) (56,59,60,64,65,70) as the open group.

Discussion

Laparoscopic pancreas surgery has been slow to evolve in comparison to other gastrointestinal surgery due to the intrinsic difficulty of operating on the pancreas and a steep learning curve involved in combining pancreas and laparoscopic surgical expertise. However, since the first descriptions of laparoscopic pancreaticoduodenectomy in 1994 and distal pancreatectomy in 1996 by Gagner and Pompe (12,13), minimally invasive pancreatectomies are being performed more frequently.

LDP has gained rapid acceptance and is associated with improved perioperative recovery, morbidity, mortality, and equivalent oncologic outcomes. In the largest single-center study to date, Song *et al*. evaluated 359 consecutive patients that underwent LDP for primarily benign disease and reported a median operative time of 195 minutes (range, 78–840 minutes), length of hospital stay of 8 days (range, 4–37 days), an overall complication rate of 12%, and a clinically significant pancreatic fistula occurring in 7% of patients (78). More recently, Sahakyan *et al*. performed a multicenter trial and analyzed postoperative and oncological outcomes in 196 patients with pancreatic adenocarcinoma undergoing LDP. In this study, operative time averaged 220 minutes, median length of stay was 8 days (range, 2–63 days), overall complications occurred in 31.9% of

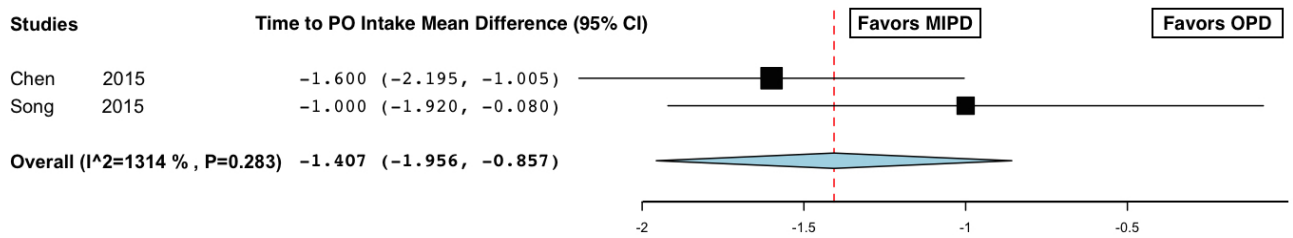

Figure 19 Time to oral intake in laparoscopic and open pancreaticoduodenectomy. MD, mean difference; CI, confidence interval; MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

patients, and a clinically significant pancreatic fistula developed in 15.7% of patients. Additionally, 83.8% of patients had negative margins and median survival was 31.3 months (79). In this review, LDP was associated with longer operative times, reduced blood loss, lower rates of positive margins, shorter length of hospital stay, earlier return of bowel function, and a shorter time to oral intake in comparison to patients undergoing open distal pancreatectomy. As demonstrated by the heterogeneity and retrospective nature of these studies there is intrinsic bias when reviewing these data. However, as a community LDP is an accepted approach for the properly selected patients. At our institution, this approach is offered to all patients regardless of histology with relative contraindications, which include: comorbidities, BMI, tumor location, size and involvement of surrounding organs. However, these are not strict criteria and selection is based on individual surgeon and patient preference.

MIPD has been much slower to evolve, as the procedure is technically very demanding with multiple anastomosis and close proximity to major vasculature. However, in the National Cancer Database, MIPD was utilized in 14% of pancreaticoduodenectomies and its use increased by 45% from 402 cases in 2010 to 581 cases in 2011 (74). Patients undergoing MIPD are a highly select group of patients with favorable anatomical and disease factors. Adam *et al*. reported factors independently associated with undergoing MIPD and found that patients with fewer comorbidities, those being treated at an academic center, having a diagnosis of NET, and presenting at an earlier stage of disease all were associated with MIPD (74). The most common contraindications to MIPD reported in the literature include neoadjuvant chemotherapy (59-62), hostile local conditions secondary to severe pancreatitis or previous complex abdominal operations (60,61,63,64), and need for potential vascular resection (59-61,63-70). At our institution the primary contraindications MIPD are pancreatitis, neoadjuvant therapy, and vein resection. But we offer this approach to all resectable disease regardless of histology. Croome *et al*. reviewed 31 patients undergoing MIPD and OPD and concluded that MIPD with vascular resection achieves similar morbidity, mortality, and oncologic outcomes compared to patients undergoing OPD with major vascular resection (72).

It is well recognized that MIPD is a lengthy procedure due to the complexity of the operation, particularly during the early learning curve associated with MIPD. Gagner *et al*. first reported a mean operative time of 8.5 hours (range, 5.5–12 hours) in 1997 (80); however, as surgeons become more adept at MIPD, operative time has decreased significantly to 295 to 515 minutes (76,81-86) with a learning curve ranging from 10 cases (83,87,88) to 50 cases (64,70). We have found, at our institution, that operative time decreased from 366 minutes to 312 minutes after the first 15 cases (89), making the efficiency of the operation equivalent to the open operation in selected patients. In addition, a distinct advantage in this review was MIPD has reduced intraoperative blood loss ranging from 65 to 300 cc (76,81-85,89). We have found this to be consistent with our experience. This is likely secondary to patient selection, however, the superior views, the need for excellent hemostasis for visualization and magnification provided by minimally invasive techniques may also contribute to the reduction of blood loss.

Post-operative complications are common after MIPD and may occur in 29% to 42% (76,81,83,84) of patients. In particular, pancreatic fistula may occur in 7% to 25.8% of patients and is potentially life threatening (76,81,83,84,86). Patients with a soft pancreas and small pancreatic duct have a greater risk of pancreatic fistula (90) and there may be a selection bias for the incidence of fistula in MIPD as benign and early malignancy tends to be selected for this approach. In

a matched analysis, Dokmak *et al*. reported a higher incidence of grade C pancreatic fistulas in the MIPD group and concluded that MIPD should only be considered in patients with a low risk of pancreatic fistula (60). In this review, patients in the MIPD group had similar overall complication rates and pancreatic fistula rates compared to OPD. In our experience with MIPD, although the majority of patients fit the criteria of a small duct and soft gland, the pancreatic grade C fistula rate was 7% and is comparable to OPD.

Prognostic factors that influence long-term outcome following PD include margin status, the number of nodes harvested, LN metastasis, grade of tumor differentiation, and vascular involvement (91,92). The accuracy of nodal staging is critically dependent on the number of LNs examined and 13 to 16 LNs are recommended (93). In the literature, LN yield in patients undergoing MIPD ranges from 7 to 18 LNs (76,80-82,84) and 0% to 11% of patients have positive margins (76,81,83,84). In this review, the mean number of LNs retrieved and margin status was similar between the open and minimally invasive techniques. Importantly, patients undergoing MIPD may be more likely to receive adjuvant chemotherapy (64,67). Additionally, minimally invasive surgery may offer distinct immunologic advantages in comparison to open operations including reduced stress of operation, attenuated impairment of the immune system, and reduced recurrence of malignancy (2,94,95).

Minimally invasive pancreatectomies may improve post-operative recovery. The length of hospital stay in patients undergoing MIPD ranges from 7 to 22 days (76,80,81,83-85) and return of bowel function has been reported to occur within 3.5 to 5.5 days (81,84). In this review, MIPD had a shorter length of hospital stay, earlier return of bowel function, and a shorter time to oral intake comparison to the open groups. We currently have ongoing quality of life studies to better understand the impact of MIPD.

There are significant limitations to the articles included in this review. In particular, there is a strong selection bias in selecting patients to undergo laparoscopic pancreatectomy versus open. Patients selected for laparoscopic techniques likely have differences in patient age, co-morbidities, tumor size, malignant features, BMI, vessel involvement, and history of abdominal operations that may result in a difficult dissection laparoscopically. These variables may lead to non-valid inferences in the outcomes associated with laparoscopic surgery. Further, the results in this review are likely due in part to publication bias in which studies that demonstrate negative findings such as an increase in morbidity and mortality in the laparoscopic group are likely to not be published. Additionally, there is a significant amount of heterogeneity in the studies included in this review. Although we attempted to identify differences in study parameters that may have led to this heterogeneity, it is a limitation inherent to systematic reviews and meta-analysis and the results must be interpreted with caution. Moreover, data published from high-volume institutions may be less generalizable to institutions that perform fewer minimally invasive cases.

Conclusions

In conclusion, this review and analysis of the available literature suggests that laparoscopic pancreatectomies are feasible, safe, reduce blood loss, improve perioperative recovery, and provide equivalent oncologic outcomes to open resection. The LDP experience is more mature than the laparoscopic pancreaticoduodenectomy experience. As experience increases there may be a change in other outcome endpoints. Even though it would be challenging with single institutional volumes, further investigation with collaborative randomized controlled trials is needed to avoid selection bias and control for confounding factors that are inherent to this type of analysis.

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Footnote

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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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