REVIEW ARTICLE

Minimally invasive versus open distal pancreatectomy: an individual patient data meta-analysis of two randomized controlled trials

Maarten Korrel[1], Frederique L. Vissers[1], Jony van Hilst[1,2], Thijs de Rooij[1], Marcel G. Dijkgraaf[3], Sebastiaan Festen[2], Bas Groot Koerkamp[4], Olivier R. Busch[1], Misha D. Luyer[5], Per Sandström[6], Mohammad Abu Hilal[7,8], Marc G. Besselink[1#], Bergthor Björnsson[6,#] for the International Minimally Invasive Pancreatic Resection Trialists Group

[1]Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, [2]Department of Surgery, OLVG Oost, Amsterdam, [3]Clinical Research Unit, Amsterdam UMC, University of Amsterdam, [4]Department of Surgery, Erasmus University Medical Center, Rotterdam, [5]Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands, [6]Department of Surgery and Clinical and Experimental Medicine, Linköping University, Linköping, Sweden, [7]Department of Surgery, Southampton University Hospital NHS Foundation Trust, Southampton, United Kingdom, and [8]Department of General Surgery, Instituto Ospedaliero Fondazione Poliambulanza, Brescia, Italy

Abstract

Background: Minimally invasive distal pancreatectomy (MIDP) has been suggested to reduce postoperative outcomes as compared to open distal pancreatectomy (ODP). Recently, the first randomized controlled trials (RCTs) comparing MIDP to ODP were published. This individual patient data meta-analysis compared outcomes after MIDP versus ODP combining data from both RCTs.

Methods: A systematic literature search was performed to identify RCTs on MIDP vs. ODP, and individual patient data were harmonized. Primary endpoint was the rate of major (Clavien-Dindo $\geq$ III) complications. Sensitivity analyses were performed in high-risk subgroups.

Results: A total of 166 patients from the LEOPARD and LAPOP RCTs were included. The rate of major complications was 21% after MIDP vs. 35% after ODP (adjusted odds ratio 0.54; p = 0.148). MIDP significantly reduced length of hospital stay (6 vs. 8 days, p = 0.036), and delayed gastric emptying (4% vs. 16%, p = 0.049), as compared to ODP. A trend towards higher rates of postoperative pancreatic fistula was observed after MIDP (36% vs. 28%, p = 0.067). Outcomes were comparable in high-risk subgroups.

Conclusion: This individual patient data meta-analysis showed that MIDP, when performed by trained surgeons, may be regarded as the preferred approach for distal pancreatectomy. Outcomes are improved after MIDP as compared to ODP, without obvious downsides in high-risk subgroups.

Received 25 May 2020; accepted 29 October 2020

Correspondence

Marc G. Besselink, Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, PO Box 22660, 1100 DD, the Netherlands. E-mail: m.g.besselink@amsterdamumc.nl

Introduction

Since the introduction of minimally invasive distal pancreatectomy (MIDP) in 1994 by Cuschieri et al.,[1] the implementation of this technique has been slow.[2] The slow implementation rate could be related to the challenging nature of MIDP and uncertainty about the clinical benefits as compared to open distal pancreatectomy (ODP).

Numerous non-randomized studies have reported on short-term outcomes after MIDP as compared to ODP, and suggested less postoperative complications, less blood loss and shorter hospital stay as main benefits.[3–9] These benefits were confirmed by two recent randomized controlled trials on MIDP vs. ODP in specialized centers in the Netherlands and Sweden.[10,11] Both trials showed shorter total length of hospital stay and less blood loss in the minimally invasive groups. Individually, however, these trials were underpowered for assessing potential differences in major postoperative complications between MIDP and ODP.[10,11]

Combining data from both trials in an individual patient data meta-analysis (IPDMA) would increase their external

[#] Shared senior authorship.

validity to provide a more robust insight in differences between MIDP and ODP. This is mostly achieved by adjusting the analyses for confounding factors that are not equally distributed across treatment groups. Besides, patient level data would allow for sensitivity analyses in different high-risk subgroups and regression analyses, as called for in the recent International Guidelines on Minimally Invasive Pancreatic Resection (IG-MIPR).[12]

The primary aim of the present study was to compare the proportion of major postoperative complications between MIDP vs. ODP, using patient level data from recent randomized controlled trials. Sensitivity analyses to assess treatment effects across pre-specified high-risk subgroups in which concerns about MIDP may exist were also performed.

Methods

Study design

This study was designed as an IPDMA and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Patient Data.[13] The PRISMA-IPD checklist can be found as supplementary file. The protocol was developed before the start of the reviewing process and was accepted for registration to PROSPERO (CRD42020151464) on January 22, 2020.

Study identification, search strategy and selection criteria

During the recruitment phase of the LAPOP and LEOPARD trials, the principal investigators (BB and MGB) agreed to perform this IPDMA and combine individual patient data after publication of both trials. To identify other possibly published randomized trials, a systematic literature search in the PubMed and Embase databases and WHO Trial Registry Database was performed on January 22, 2020. Only randomized trials written in English with available patient level data published between January 1, 2000 and January 22, 2020 were considered for eligibility. Terms used for this systematic literature search included "distal pancreatectomy OR left pancreatectomy OR pancreatic tail resection OR pancreatosplenectomy" AND "laparoscopy OR minimally invasive surgery".

Two authors independently examined titles, abstracts, and full-texts of studies identified by the search strategy. Studies were excluded if the study was not a randomized trial, or if the study did not focus on MIDP vs. ODP. Conflicts or uncertainties were resolved by discussion between the two reviewers. The second version of the Cochrane Collaboration Tool for Risk of Bias assessment in Clinical Trials was used to assess the risk of bias in the included studies.[14] Two reviewers assessed the included studies for risk of bias independently, and conflicts were resolved by discussion between the two reviewers.

Collection and harmonization of individual patient data

Upon the completion of screening, principal investigators of the eligible studies were contacted with the study protocol describing the objectives and procedures of this IPDMA. After approval by the investigators, the trial protocols and data dictionaries were compared to identify variables that needed recoding. The study coordinator (MK) then provided the principal investigators with a standardized database containing the variables of interest with their definitions. After anonymization of patient data, these were sent to the study coordinator (MK), who then performed data-checks for wrong entries, duplicate and non-logical values, and missing data. The individual trial teams were contacted to resolve any queries that emerged during the data checks. The final dataset specification is shown in Table S1 in the Supplementary File.

Data collection and definitions

Data collection for the variables of interest was performed as per protocol of the primary studies, i.e. by standardized case report forms. Primary and secondary outcomes were collected from randomization up to 90 days postoperatively.

The primary study outcome was the rate of major complications (Clavien-Dindo score III or higher).[15] Secondary outcomes included length of hospital stay, readmissions, reinterventions, pancreatic surgery specific complications, and 90-day mortality. Comorbidities were categorized by calculating the Charlson-Comorbidity Index (CCI).[16] CCI index of five and higher was considered as severe comorbidity. Body Mass Index (BMI) of $\geq$25 kg/m^2 was considered overweight. Clinically relevant postoperative pancreatic fistula (POPF),[17] delayed gastric emptying (DGE),[18] and postpancreatectomy hemorrhage[19] were defined as grade B/C complications based on the International Study Group on Pancreatic Surgery definitions. Total length of hospital stay was defined as the days of hospital admission during the primary stay, plus the length of readmissions within 90 days after surgery.

Statistical analyses

Statistical analyses in this IPDMA were performed according to the "one-stage" approach as proposed by the PRISMA-IPD statement.[13] Herein, individual patient data from all trials were modelled simultaneously whilst accounting for clustering of patients within trials (i.e. stratifying for trial).

All analyses were performed according to the intention-to-treat principle. Since different inclusion criteria among the included studies might introduce bias during analyses, generalized linear model analysis were performed whilst stratifying for trial. Trial was used as fixed effect rather than a random effect, since treatment options were similar and all outcomes have been consistently measured following standardized definitions in both trials. Treatment effects of MIDP were adjusted

for pre-specified baseline covariates of sex, age, BMI, CCI, ASA score, pre-operative pancreatitis, type of disease (malignant vs. non-malignant), and prior abdominal surgery.

The treatment effects of MIDP were analyzed in pre-specified subgroups of overweight (BMI $\geq$25 kg/m^2), severe comorbidities (CCI $\geq$5), and malignant disease as called for in the recent IG-MIPR guidelines.[12] The same hierarchical regression structure with the same pre-specified covariates as described above was used. Dichotomous outcomes are reported as odds ratios and 95% confidence intervals (CIs), whereas continuous outcomes are reported as mean differences and 95%CI.

Furthermore, additional regression analyses were performed to evaluate the treatment effect of MIDP on POPF (grade B/C) and DGE (grade B/C). The aforementioned baseline covariates were included in univariable analysis. Covariates with $p < 0.2$ in the univariable analysis were included in a multivariable regression model, with forced entry of surgical technique (backward selection). Results are presented as odds ratios (OR) and 95%CIs. Finally, a sensitivity analysis excluding patients who eventually did not undergo resection due to intraoperative irresectability was performed.

Analyses were performed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Orchard Road Armonk, New York, US). Statistical significance was defined as a P value less than 0.05.

Results

Study selection

The literature search identified a total of 2406 studies, whereas 172 studies were found in the WHO Trial Registry Database. Two trials in the WHO Trial Registry Database were published; four other trials were recruiting patients at the time of analysis (ISRCTN44897265, NCT03957135, NCT03792932, DRKS00014011), and one identified study was prematurely terminated (NCT00988793). An observational study design was the most common reason for exclusion during the reviewing process (n = 2366), whereas 165 trials identified in the WHO Trial Registry Database did not fit the inclusion criteria. Eventually, the screening process left two studies for inclusion: the LAPOP and LEOPARD trials.[10,11] Fig. 1 shows the CONSORT Diagram of the systematic review. No systematic reviews and meta-analyses on this subject were registered in PROSPERO at the start of the reviewing process.

Eligible randomized trials

The protocols including eligibility criteria of both trials have been published previously.[20,21] Country specific and local ethical approval for the original studies was obtained at the individual trial sites by the principal investigators (LEOPARD trial NL52031.018.15; LAPOP trial 2015-39-31). The LEOP-

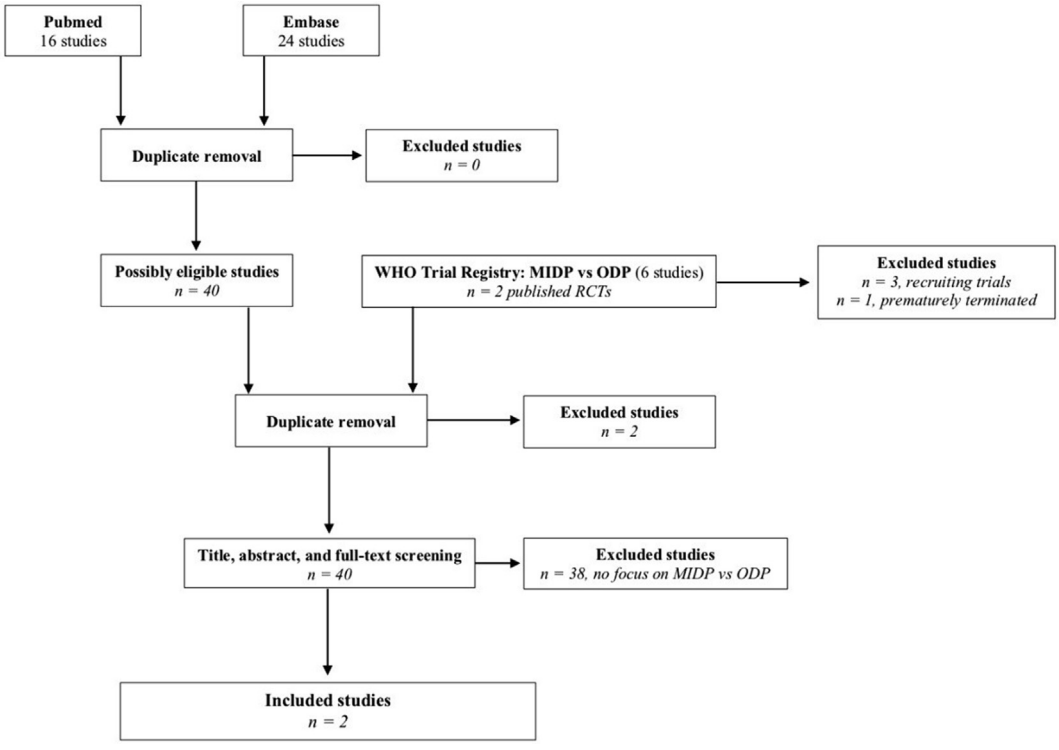

Figure 1 Flow diagram: Only randomized controlled trials

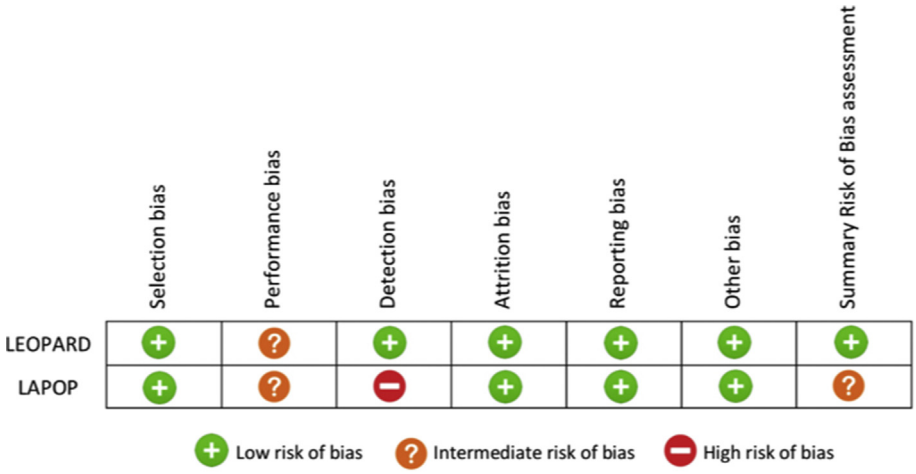

Figure 2 Risk of bias assessment of the included LAPOP and LEOPARD trials

ARD trial was performed among 14 Dutch centers that had all participated in a nationwide training program for laparoscopic distal pancreatectomy.[22] The LAPOP trial was performed by specifically trained surgeons from a single Swedish hospital.[23]

Risk of bias assessment showed that both studies had either low or intermediate risk of bias. Both trials had intermediate risk at the domain of performance bias, as not all outcome assessors were blinded. The risk of detection bias was higher in the LAPOP trial, since patients were not blinded for treatment allocation (i.e. the absence of blinding could have influenced time to functional recovery in these patients). The risk of bias assessment is shown in Fig. 2. No issues were identified in checking the individual patient data on wrong entries, duplicate and non-logical values, and missing data. The models used for outcome assessment were found to be a good fit to the data. The Supplementary Statistical Methods in the Supplementary File report the results of the goodness of fit assessment.

Study population

A total of 166 patients were randomized to MIDP (n = 80) or ODP (n = 86) within a mean inclusion period of 13 months per center. The majority of patients (n = 108) were randomized in the LEOPARD trial, whereas 58 patients were randomized in the LAPOP trial. Baseline characteristics were comparable as shown in Table 1. Overall, four patients did not undergo resection due to intraoperative metastases, and two patients underwent a different surgical procedure based on unexpected intraoperative findings

Table 1 Baseline characteristics

Characteristic[a]	MIDP (n = 80)	ODP (n = 86)	P-value
Age – mean	63.7 ± 12.7	62.8 ± 12.4	0.658
Female sex – no./total no. (%)	41/80 (51.2)	45/86 (52.3)	0.890
Malignant disease – no./total no. (%)	36/80 (45.0)	38/86 (44.2)	0.978
Tumor size on imaging – mean	29.5 ± 14.4	33.0 ± 20.0	0.232
Prior abdominal surgery – no./total no. (%)	37/80 (46.3)	41/86 (47.7)	0.854
Body mass index – mean	26.9 ± 5.7	27.0 ± 4.9	0.888
Charlson comorbidity index			
Mild comorbidity (CCI 1–2)	21/80 (26.3)	24/86 (27.9)	0.939
Moderate comorbidity (CCI 3–4)	29/80 (36.3)	29/86 (33.7)	
Severe comorbidity (≥5)	30/80 (37.5)	33/86 (38.4)	
ASA score			
ASA I	20/80 (25.0)	15/86 (17.4)	0.191
ASA II	40/80 (50.0)	55/86 (63.9)	
ASA III	20/80 (25.0)	16/86 (18.6)	

[a] Means are presented with standard deviation (±SD). MIDP denotes minimally invasive distal pancreatectomy; ODP open distal pancreatectomy; ASA American College of Anesthesiologists.

Table 2 Postoperative outcomes during hospital stay and thereafter until 90 days

Outcomes[a]	MIDP (n = 80)	ODP (n = 86)	Incremental effect (95%CI)[b]	P-value
Major complications – no. (%)	17/80 (21.3)	30/86 (34.9)	0.54 (0.24–1.24)	0.148
Operative time – mean (SD)	187.4 ± 84.9	162.7 ± 63.9	19.8 (–1.2 to 40.8)	0.064
Blood loss (ml) – mean (SD)	203.6 ± 284.7	449.8 ± 577.6	–227.7 (–374.1 to –81.3)	0.002
Conversion – no. (%)[e]	5/80 (6.3)	NA	NA	NA
Length of hospital stay				
Primary admission – days				
Mean	6.1 ± 5.8	8.2 ± 6.3	–2.1 (–1.0 to –0.13)	0.036
ICU admission – days				
Admitted to ICU – no. (%)	7/80 (8.8)	12/86 (14.0)	0.68 (0.24–1.92)	0.466
Mean[c]	1.7 ± 1.9	3.9 ± 6.8	–1.8 (–8.5 to 4.9)	0.603
During readmissions – days				
Readmitted – no. (%)	19/80 (23.8)	21/86 (24.4)	0.76 (0.32–1.79)	0.528
Mean	8.5 ± 7.1	11.3 ± 12.0	–4.8 (–11.7 to 2.1)	0.174
Total length of stay - days[d]				
Mean	9.0 ± 8.5	12.0 ± 10.2	–3.7 (–6.8 to –0.6)	0.019
POPF Grade B/C – no. (%)	29/80 (36.3)	24/86 (27.9)	2.18 (0.95–5.04)	0.067
DGE Grade B/C – no. (%)	3/80 (3.8)	14/86 (16.3)	0.26 (0.07–0.99)	0.049
PPH Grade B/C – no. (%)	2/80 (2.5)	2/86 (2.3)	1.12 (0.15–8.27)	0.910
Reinterventions – no. (%)	17/80 (21.3)	28/86 (32.6)	0.59 (0.26–1.34)	0.207
Radiological reintervention – no. (%)	16/80 (20.0)	16/86 (18.6)	1.29 (0.51–3.24)	0.592
Endoscopic reintervention – no. (%)	6/80 (7.5)	17/86 (19.8)	0.30 (0.10–0.91)	0.033
Surgical reintervention – no. (%)	2/80 (2.5)	4/86 (4.7)	0.74 (0.12–4.58)	0.741
Mortality – no. (%)[e]	0/80 (0.0)	2/86 (2.3)	NA	NA

[a] Means are presented with standard deviations (±SD). MIDP denotes minimally invasive distal pancreatectomy; ODP open distal pancreatectomy; CI confidence interval; OR odds ratio; IQR interquartile range; ICU intensive care unit; POPF postoperative pancreatic fistula; DGE GRADE B/C delayed gastric emptying; PPH postpancreatectomy hemorrhage; NA not available.
[b] Incremental effects are difference in means and adjusted odds ratios. Adjusted odds ratios are adjusted for age, gender, disease type, prior abdominal surgery, Charlson Index, pancreatitis, BMI, ASA score, and trial cohort.
[c] Means and medians only calculated for unplanned admission.
[d] Total length of stay is the sum of days admitted during the primary admission and the length of stay during readmission within 90 days.
[e] The odds ratios and p-values are not calculated due to limited numbers.

(i.e. open enucleation or laparoscopic adrenalectomy). Eventually, 76 patients underwent MIDP, whereas 84 patients underwent ODP.

Outcomes

Outcomes are presented in Table 2. The rate of major complications within 90 days postoperatively was comparable after MIDP and ODP (21% vs 35%). The adjusted odds ratio was 0.54 (95%CI 0.24 to 1.24, p = 0.148), with a relative risk reduction of 40%.

Patients operated in the MIDP group had on average 227 ml less blood loss (p = 0.002) than ODP, whereas there was a trend towards longer operative time in the MIDP group (187 vs 163 min; p = 0.064). The conversion rate in the MIDP group was 3%. The average length of hospital stay during primary admission was reduced with 2.1 days (95%CI -1.0 to −0.13, p = 0.036) in the MIDP group. Besides, the rates of DGE grade B/C (4% vs. 16%, p = 0.049) and endoscopic reinterventions (8% vs. 20%, p = 0.033) were significantly lower after MIDP as compared to ODP. Other secondary outcomes, including POPF, did not differ significantly.

Sensitivity analyses in high-risk subgroups

Results of the sensitivity analyses are shown in Supplementary Tables S2 until S5. In overweight patients (49 MIDP vs 56 ODP), severe comorbidity (30 MIDP vs 33 ODP), and malignancy (36 MIDP vs 38 ODP), the reduction in major complication rates varied between 7 and 15%, but did not reach significance. In the subgroup of overweight patients, the POPF grade B/C rate was almost three-fold higher as compared to normal weight patients (OR 6.69; p = 0.001) and significantly more POPF grade B/C were found after MIDP as compared to ODP (51% vs. 34%, p = 0.022). In overweight patients, MIDP procedures were on average 27 min (95%CI 0.3 to 53.0, p = 0.048) longer than ODP procedures. In patients with malignancy, radical (R0 ≥ 1 mm between tumor and margin)

resection rates (67% vs. 61%, p = 0.639) and number of retrieved lymph nodes (mean 9.5 vs 10.3 nodes, p = 0.819) were similar, whereas blood loss was significantly less in MIDP patients (−328 ml, p = 0.019).

Regression analyses for pancreatic fistula and delayed gastric emptying

Outcomes of the regression analyses are presented in Tables S6 and S7. For predicting POPF grade B/C, overweight, prior abdominal surgery, and ASA-score had a p-value less than 0.2 and thus were selected for multivariable analysis. Surgical technique was entered using backward selection. At multivariable analysis, MIDP was not associated with an increased risk (p = 0.163), whereas overweight (p = 0.001) and prior abdominal surgery (p = 0.009) were significantly associated with POPF grade B/C. For predicting DGE grade B/C, prior abdominal surgery, preoperative pancreatitis, and surgical technique had a p-value less than 0.2. At multivariable analysis, MIDP was associated with lower rates of DGE grade B/C (p = 0.018).

Discussion

This first meta-analysis of individual patient data from two RCTs on MIDP versus ODP showed comparable rates of major postoperative complications. MIDP reduced the rates of DGE grade B/C and endoscopic reinterventions, as well as blood loss and hospital stay. Outcomes were not impaired after MIDP in the pre-specified high-risk subgroups.

This IPDMA confirmed the superiority of MIDP over ODP as suggested by previous reports and the included trials.[4–8] Moreover, the IPDMA design allowed for sensitivity analyses in prespecified subgroups and regression analyses to answer questions beyond the scope of the original trials, thus presenting relevant evidence. Major complications were not increased after MIDP in the three high-risk subgroups, thus supporting the IGMIPR recommendations that MIDP is not contraindicated in these subgroups.[12] Besides, the benefits found in the present study could lead to comparable or even improved cost-effectiveness as suggested in previous reports.[24–26] A post-hoc sample size calculation revealed that with a power of 80%, an alpha of 0.05, and the 14% difference found in the present study, the sample size would require 320 (160 vs. 160) patients in a randomized controlled trial. Although the present study did not reach these numbers, it seemed worthwhile to combine results of the two RCTs. Future studies should consider the IPDMA design including other RCTs (such as DIPLOMA, DISPATCH 2) to achieve the required sample size for this analysis.

An important note should be made concerning the differences present between the pooled outcomes of the individual studies, such as operative time and blood loss. Despite the fact that distal pancreatectomies are mostly performed by expert surgeons, differences could still exist among these surgeons as shown by the individual trial results. These differences could be explained by the fact that some LEOPARD surgeons performed the procedures rather early in their learning curve, leading to less advantageous outcomes in these patients as opposed by a single surgeon performing all MIDPs in the LAPOP study. Moreover, as per the design of this study, standardization of surgical technique could not be warranted. Subsequent heterogeneity in outcomes might have occurred in the present study. However, individual patient data allowed for adjusting the analyses for such confounders, thus limiting heterogeneity. Therefore, outcomes of this study have increased external validity, and are more applicable to other centers as compared to outcomes presented by the individual studies. Besides, it seems unlikely that the differences in learning curve would negatively influence the current benefits of MIDP as presented in this IPDMA. Despite the fact that length of hospital stay varies greatly between countries, this variable was similar between the two included trials indicating that combining the data should be considered valid.

Interestingly, a trend towards higher POPF B/C rates but comparable rates of percutaneous catheter drainage and major complications after MIDP were found. This difference is most likely explained by differences in patient treatment between studies, especially since pancreas transection method, drain amylase levels on day 3, and the rate of percutaneous catheter drainage were identical in MIDP and ODP in both studies. In the LEOPARD trial, patients were discharged home if they were functionally recovered even when drain amylase levels were high. Therefore, several MIDP patients were discharged home with the surgical drain in situ. A subsequent delayed removal of the surgical drain during the outpatient visits beyond postoperative day 21 would lead to the diagnosis of a clinically relevant pancreatic fistula grade B according to the updated definitions (19 MIDP vs. 11 ODP patients).[17] In contrast, patients in the ODP group often remained in the hospital long enough to have a second or third measurement of drain amylase and subsequent in-hospital drain removal. Future prospective studies should confirm that early outpatient visits after discharge with drain removal,[27] or alternatively, a future no-drain-policy[28] could solve this issue.

Although the POPF grade B/C rate was the most frequent complication and slightly higher after MIDP, a lower rate of major complications was found after MIDP as compared to ODP. Since percutaneous catheter drainage rates for POPF were identical, this could be explained by significantly lower rates of endoscopic reinterventions after MIDP as compared to ODP. The most frequently noted reason for endoscopic reintervention was nasojejunal feeding tube placement for DGE, which was also significantly lower after MIDP as compared to ODP. It is therefore important to note that this could have confounded the rates of major complications between MIDP and ODP. These differences in DGE grade B/C and endoscopic reinterventions could be explained by differences in tissue handling and gastric manipulation between the techniques. Even though the rates of DGE grade B/C were lower after MIDP, the overall rate of DGE grade B/C is arguably high and was higher as compared to previous

reports.[29] This difference might be due to underreporting in previous retrospective studies.

Although oncological outcomes in the relatively small subgroup of malignancies seemed comparable, randomized studies are necessary to provide clear insight in the role of MIDP in this group of patients.[30,31] Currently, several trials are recruiting patients undergoing MIDP or ODP specifically for pancreatic cancer, including the DIPLOMA trial (ISRCTN44897265; www.e-mips.com) in 38 centers from Europe and the USA. Furthermore, a multicenter trial from South-Korea (NCT03957135), a monocenter trial from China (NCT03792932) and a German (DRKS00014011) trial are registered, comparing MIDP to ODP for any indication or pancreatic ductal adenocarcinoma.

Unlike the results of numerous retrospective observational studies supporting the use of MIDP, results from this meta-analysis of individual patient data rely exclusively on random assignment. Consequently, biases inherent to retrospective studies, most importantly selection bias, are avoided. Nonetheless, several limitations should be considered. First, data on functional recovery could not be pooled, since the individual studies used slightly different definitions for this endpoint (see Supplementary Methods in the Supplementary File). In both individual studies, however, time to functional recovery was shorter after MIDP. Second, some sensitivity analyses still had limited statistical power due to low patient numbers. Third, none of the included studies were assessor blinded, which might have introduced performance bias.

Conclusions

This individual patient data meta-analysis of available RCTs showed that MIDP, when performed by trained surgeons, may be regarded as the preferred approach for distal pancreatectomy. Outcomes are improved after MIDP, as compared to ODP, without obvious downsides in high-risk subgroups. Currently ongoing trials will confirm the role of MIDP in patients with ductal adenocarcinoma.

Acknowledgements

We thank all investigators of the LEOPARD and LAPOP trials for their contributions to the original trials. All authors of the original studies are presented in the Collaborators chapter in the Supplementary File.

Funding source

A research grant for investigator-initiated studies was received from Ethicon Endo-surgery (Johnson & Johnson Family of Companies, New Brunswick, NJ) for the LEOPARD trial. Funding was received from the research organizations FORSS and ALF for the LAPOP trial.

Conflicts of interest

None declared.

References

1. Cuschieri A. (1994) Laparoscopic surgery of the pancreas. *J R Coll Surg Edinb* 39:178–184.
2. Abu Hilal M, Takhar AS. (2013) Laparoscopic left pancreatectomy: current concepts. *Pancreatology* 13:443–448.
3. de Rooij T, Klompmaker S, Abu Hilal M, Kendrick ML, Busch OR, Besselink MG. (2016) Laparoscopic pancreatic surgery for benign and malignant disease. *Nat Rev Gastroenterol Hepatol* 13: 227–238.
4. Drymousis P, Raptis DA, Spalding D, Fernandez-Cruz L, Menon D, Breitenstein S *et al*. (2014) Laparoscopic versus open pancreas resection for pancreatic neuroendocrine tumours: a systematic review and meta-analysis. *HPB* 16:397–406.
5. Jin T, Altaf K, Xiong JJ, Huang W, Javed MA, Mai G *et al*. (2012) A systematic review and meta-analysis of studies comparing laparoscopic and open distal pancreatectomy. *HPB* 14:711–724.
6. Jusoh AC, Ammori BJ. (2012) Laparoscopic versus open distal pancreatectomy: a systematic review of comparative studies. *Surg Endosc* 26:904–913.
7. Nigri GR, Rosman AS, Petrucciani N, Fancellu A, Pisano M, Zorcolo L *et al*. (2011) Metaanalysis of trials comparing minimally invasive and open distal pancreatectomies. *Surg Endosc* 25:1642–1651.
8. Venkat R, Edil BH, Schulick RD, Lidor AO, Makary MA, Wolfgang CL. (2012) Laparoscopic distal pancreatectomy is associated with significantly less overall morbidity compared to the open technique: a systematic review and meta-analysis. *Ann Surg* 255:1048–1059.
9. Richardson J, Di Fabio F, Clarke H, Bajalan M, Davids J, Abu Hilal M. (2015) Implementation of enhanced recovery programme for laparoscopic distal pancreatectomy: feasibility, safety and cost analysis. *Pancreatology* 15:185–190.
10. de Rooij T, van Hilst J, van Santvoort H, Boerma D, van den Boezem P, Daams F *et al*. (2019) Minimally invasive versus open distal pancreatectomy (LEOPARD): a multicenter patient-blinded randomized controlled trial. *Ann Surg* 269:2–9.
11. Bjornsson B. (2020) Laparoscopic distal pancreatectomy has a shorter hospital stay than open surgery: randomized clinical trial (LAPOP). *Br J Surg* 107:1281–1288.
12. Asbun HJ, Moekotte AL, Vissers FL, Kunzler F, Cipriani F, Alseidi A *et al*. (2019) The miami international evidence-based Guidelines on minimally invasive pancreas resection. *Ann Surg* 271:1–14.
13. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G *et al*. (2015) Preferred reporting Items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *J Am Med Assoc* 313:1657–1665.
14. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD *et al*. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928.
15. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 240:205–213.
16. Charlson ME, Sax FL, MacKenzie CR, Braham RL, Fields SD, Douglas RG, Jr. (1987) Morbidity during hospitalization: can we predict it? *J Chron Dis* 40:705–712.
17. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M *et al*. (2017) The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Surgery* 161:584–591.

18. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR *et al*. (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 142:761–768.
19. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ *et al*. (2007) Postpancreatectomy hemorrhage (PPH): an international study group of pancreatic surgery (ISGPS) definition. *Surgery* 142:20–25.
20. Bjornsson B, Sandstrom P, Larsson AL, Hjalmarsson C, Gasslander T. (2019) Laparoscopic versus open distal pancreatectomy (LAPOP): study protocol for a single center, nonblinded, randomized controlled trial. *Trials* 20:356.
21. de Rooij T, van Hilst J, Vogel JA, van Santvoort HC, de Boer MT, Boerma D *et al*. (2017) Minimally invasive versus open distal pancreatectomy (LEOPARD): study protocol for a randomized controlled trial. *Trials* 18:166.
22. de Rooij T, van Hilst J, Boerma D, Bonsing BA, Daams F, van Dam RM *et al*. (2016) Impact of a nationwide training program in minimally invasive distal pancreatectomy (LAELAPS). *Ann Surg* 264: 754–762.
23. Hasselgren K, Halldestam I, Fraser MP, Benjaminsson Nyberg P, Gasslander T, Bjornsson B. (2016) Does the introduction of laparoscopic distal pancreatectomy jeopardize patient safety and well-being? *Scand J Surg* 105:223–227.
24. Fisher AV, Fernandes-Taylor S, Schumacher JR, Havlena JA, Wang X, Lawson EH *et al*. (2019) Analysis of 90-day cost for open versus minimally invasive distal pancreatectomy. *HPB* 21:60–66.
25. Joechle K, Conrad C. (2018) Cost-effectiveness of minimally invasive pancreatic resection. *J Hepatobiliary Pancreat Sci* 25:291–298.
26. van Hilst J, Strating EA, de Rooij T, Daams F, Festen S, Groot Koerkamp B *et al*. (2019) Costs and quality of life in a randomized trial comparing minimally invasive and open distal pancreatectomy (LEOPARD trial). *Br J Surg* 106:910–921.
27. de Rooij T, Cipriani F, Rawashdeh M, van Dieren S, Barbaro S, Abuawwad M *et al*. (2017) Single-surgeon learning curve in 111 laparoscopic distal pancreatectomies: does operative time tell the whole story? *J Am Coll Surg* 224:826–832 e1.
28. Van Buren G, 2nd, Bloomston M, Schmidt CR, Behrman SW, Zyromski NJ, Ball CG *et al*. (2017) A prospective randomized multicenter trial of distal pancreatectomy with and without routine intraperitoneal drainage. *Ann Surg* 266:421–431.
29. de Rooij T, Jilesen AP, Boerma D, Bonsing BA, Bosscha K, van Dam RM *et al*. (2015) A nationwide comparison of laparoscopic and open distal pancreatectomy for benign and malignant disease. *J Am Coll Surg* 220:263–270 e1.
30. van Hilst J, Korrel M, de Rooij T, Lof S, Busch OR, Groot Koerkamp B *et al*. (2019) Oncologic outcomes of minimally invasive versus open distal pancreatectomy for pancreatic ductal adenocarcinoma: a systematic review and meta-analysis. *Eur J Surg Oncol* 45:719–727.
31. van Hilst J, de Rooij T, Klompmaker S, Rawashdeh M, Aleotti F, Al-Sarireh B *et al*. (2019) Minimally invasive versus open distal pancreatectomy for ductal adenocarcinoma (DIPLOMA): a pan-European propensity score matched study. *Ann Surg* 269:10–17.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.10.022.