Minimally Invasive versus Open Distal Pancreatectomy for Ductal Adenocarcinoma (DIPLOMA)

A Pan-European Propensity Score Matched Study

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Objective: The aim of this study was to compare oncological outcomes after minimally invasive distal pancreatectomy (MIDP) with open distal pancreatectomy (ODP) in patients with pancreatic ductal adenocarcinoma (PDAC).
Background: Cohort studies have suggested superior short-term outcomes of MIDP vs. ODP. Recent international surveys, however, revealed that surgeons have concerns about the oncological outcomes of MIDP for PDAC.
Methods: This is a pan-European propensity score matched study including patients who underwent MIDP (laparoscopic or robot-assisted) or ODP for PDAC between January 1, 2007 and July 1, 2015. MIDP patients were matched to ODP patients in a 1:1 ratio. Main outcomes were radical (R0) resection, lymph node retrieval, and survival.
Results: In total, 1212 patients were included from 34 centers in 11 countries. Of 356 (29%) MIDP patients, 340 could be matched. After matching, the MIDP conversion rate was 19% (n = 62). Median blood loss [200 mL (60–400) vs 300 mL (150–500), $P = 0.001$] and hospital stay [8 (6–12) vs 9 (7–14) days, $P < 0.001$] were lower after MIDP. Clavien-Dindo grade $\geq$3 complications (18% vs 21%, $P = 0.431$) and 90-day mortality (2% vs 3%, $P > 0.99$) were comparable for MIDP and ODP, respectively. R0 resection rate was higher (67% vs 58%, $P = 0.019$), whereas Gerota's fascia resection (31% vs 60%, $P < 0.001$) and lymph node retrieval [14 (8–22) vs 22 (14–31), $P < 0.001$] were lower after MIDP. Median overall survival was 28 [95% confidence interval (CI), 22–34] versus 31 (95% CI, 26–36) months ($P = 0.929$).
Conclusions: Comparable survival was seen after MIDP and ODP for PDAC, but the opposing differences in R0 resection rate, resection of Gerota's fascia, and lymph node retrieval strengthen the need for a randomized trial to confirm the oncological safety of MIDP.

Keywords: distal pancreatectomy, laparoscopic, left pancreatectomy, minimally invasive, robot-assisted

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Minimally invasive distal pancreatectomy (MIDP) was introduced in 1994.[1] Several systematic reviews of cohort studies have suggested superior short-term outcomes of MIDP, defined as either laparoscopic or robot-assisted distal pancreatectomy (DP), as compared to open distal pancreatectomy (ODP) for non-malignant pancreatic diseases, without increasing costs.[2–11] The most important advantages of MIDP include less intraoperative blood loss and shorter postoperative hospital stay. However, the oncological safety in terms of resection margins, adequate lymphadenectomy, and survival after MIDP in the treatment of pancreatic ductal adenocarcinoma (PDAC) remains controversial.

A recent Cochrane review including 11 studies and a total of 1506 patients with PDAC of the pancreatic body or tail showed comparable rates of nonradical (R1/R2) resection margins, tumor recurrence, and survival after MIDP and ODP.[12] Importantly, randomized controlled trials were lacking and most studies were single-center and retrospective, leading to concerns about the impact of treatment allocation bias. Further concerns regarding the oncological outcomes of MIDP for patients with PDAC were raised in 2 recent international surveys.[13,14] Almost one-third of European pancreatic surgeons considered MIDP inferior to ODP regarding oncological outcomes[13] and a worldwide survey showed that 21% of pancreatic surgeons considered PDAC a contraindication for a minimally invasive aproach.[14] Surgeons may doubt whether the essential components of an adequate oncological resection during DP (ie, radical resection margins, resection of Gerota's fascia, and sufficient lymphadenectomy) are equally well obtained during MIDP compared to ODP.

In 2015, a group of European surgeons initiated the European consortium for Minimally Invasive Pancreatic Surgery (E-MIPS) to facilitate safe implementation of minimally invasive pancreatic surgery. This group designed the DIPLOMA (Distal Pancreatectomy, minimally invasive or open for malignancy) pan-European propensity score-matched study, which aims to compare short- and long-term outcomes after MIDP and ODP in patients with PDAC with a focus on resection margins, lymphadenectomy, and survival.

METHODS

This study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15] The ethics committee of the Academic Medical Center waived the need for informed consent because of the observational study design.

Design and Patients

This pan-European retrospective cohort study was performed among E-MIPS centers. All consecutive patients who underwent DP (minimally invasive or open) with a histopathological diagnosis of PDAC between January 1, 2007 and July 1, 2015 were screened for inclusion. Patients were excluded if they had a previous pancreatic resection, if distant metastases were present, if the tumor involved the celiac trunk or when the tumor only became resectable after down staging with neoadjuvant therapy. Patients were categorized according to the method of surgery: MIDP or ODP.

Definitions

MIDP was defined as laparoscopic or robot-assisted surgery. PDAC was defined according to the WHO classification of pancreatic tumors, which includes mucinous noncystic carcinomas, signet ring cell carcinomas, adenosquamous carcinomas, undifferentiated (anaplastic) carcinomas, undifferentiated carcinomas with osteoclast-like giant cells, and mixed ductal-endocrine carcinomas.[16] MIDP conversion was defined as any laparotomy for other reasons than trocar placement or specimen extraction. Postoperative complications were classified using the Clavien-Dindo classification.[17] Major complications were defined as Clavien-Dindo grade $\geq$3. The definitions for pancreatic surgery-specific complications of the International Study Group on Pancreatic Surgery (ISGPS) were used to score postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), and postpancreatectomy hemorrhage (PPH).[18–20] Only ISGPS grade B/C complications were collected. Surgical site infection (SSI) was defined using the Centers for Disease Control and Prevention definition.[21] Resection margins, including transection and circumferential margins, were categorized into: R0 (distance margin to tumor $\geq$1 mm), R1 (distance margin to tumor <1 mm), and R2 (macroscopically positive margin) according to the Royal College of Pathologists definition.[22]

Data Collection

All 34 participating centers received a blank database containing all parameters (including definitions) of interest. The data were collected locally by each participating center and combined centrally by the study coordinators. All participating centers also received a survey regarding the method of local data collection (eg, type of database used) and annual volumes. Baseline characteristics collected included sex, age, body mass index (BMI, kg/m^2), previous abdominal surgery, American Society of Anaesthesiologists (ASA) physical status, and administration of neoadjuvant chemo- and/or radiotherapy. Preoperative imaging was reviewed for tumor location, tumor size (mm), and tumor involvement of other organs. Collected outcomes were procedure type (open, minimally invasive), conversion and reason for conversion, operative time (minutes), blood loss (mL), splenectomy, resection of Gerota's fascia, adrenalectomy, additional organ resection (beyond adrenalectomy and splenectomy), vascular resection (beyond resection of the splenic vessels), tumor size (mm), overall and tumor positive lymph node retrieval, tumor and lymph node stage, involvement of resection margin, lymphovascular and perineural invasion, major complications, POPF, DGE, PPH, SSI, length of hospital stay (days), readmission, 90-day mortality, adjuvant chemotherapy, time until start adjuvant chemotherapy (days), and overall survival (months). Complications, readmissions, and mortality were all collected up to 90 days postoperatively. Overall survival was, depending on the center, either collected from patient records, municipal personal records database, or by personal contact with patient or family. All data were stored and processed anonymously.

Matching

To minimize the impact of treatment allocation bias, MIDP patients were matched to ODP patients using propensity scores. Multivariable logistic regression was performed to estimate the propensity to undergo MIDP for all patients, regardless of the actual treatment received. Propensity scores were based on baseline variables age, sex, BMI, ASA physical status, previous abdominal surgery, neoadjuvant therapy, year of surgery and tumor size, involvement of other organs, and tumor location on preoperative imaging. Nearest neighbor matching was performed in a 1:1 ratio without replacement and a caliper width of 0.01 standard deviation (SD) was specified. To be able to calculate propensity scores for all patients, missing baseline variables were imputed using single imputation based on predictive mean matching.

Statistical Analyses

Data were analyzed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY) and R Statistical Software version i386 3.3.3 (Foundation for Statistical Computing, Vienna, Austria). Analyses were performed according to the intention-to-treat principle. Before matching normally distributed continuous data are presented as means with SDs and were compared using the 2 independent samples t test. Non-normally distributed continuous data are presented as medians with interquartile ranges and were compared using the Mann-Whitney U test. Categorical data are presented as frequencies with percentages, and were compared using the Chi-square or Fisher exact test, as appropriate. Survival curves were plotted according to the Kaplan-Meier method and comparison of survival probabilities was performed using the log rank (Mantel-Cox) test and a Cox proportional hazards model. After matching, normally distributed continuous data were compared using the paired samples t test.[23] For non-normally distributed continuous data, the Wilcoxon signed rank test was used. Categorical data were compared using the McNemar's test. Comparison of survival probabilities after matching was performed using a stratified log-rank and a Cox proportional hazards model with shared frailty.[24] Sensitivity analyses were performed by excluding patients who received neoadjuvant therapy and by excluding patients who did not receive a splenectomy. To study the effect of time, a subgroup analysis was performed comparing different time intervals. A P value <0.05 was considered statistically significant.

RESULTS

Participating Centers

The survey showed that participating centers performed a median of 93 (59–165) pancreatic resections per year, including, a median of 30 (20–59) distal pancreatectomies (all indications), 14 (6–25) distal pancreatectomies for PDAC and 15 (10–26) MIDPs (all indications). Of all participating centers, 4 did not perform MIDP during the study period.

Total Cohort

In total, 1297 patients were screened, of whom 85 were excluded for reasons shown in Figure 1, leaving 1212 patients for analysis. The total cohort consisted of 356 MIDPs (29%) of which 16 (4%) were robot-assisted distal pancreatectomies, as shown in Table 1 (total cohort). Tumor involvement of other organs was less often seen on preoperative imaging in the MIDP group (6% vs 13%, $P = 0.001$) and less neoadjuvant chemotherapy was used in the MIDP group (3% vs 11%, $P \leq 0.001$). Intraoperative outcomes are presented in Table 2 (total cohort). Conversion from MIDP to ODP occurred in 65 patients (18%). Postoperative length of hospital stay was shorter after MIDP [median 8 (5–12) vs 9 (7–14) days, $P \leq 0.001$]. All pathology outcomes are shown in Table 3 (total cohort). The median amount of retrieved lymph nodes was lower for MIDP compared with ODP [14 (8–22) vs 18 (11–28) nodes, $P < 0.001$] (Table 3, total cohort). The R0 resection rate was higher after MIDP compared with ODP (67% vs 60%, $P = 0.015$). All postoperative outcomes are shown in Table 4 (total cohort). The overall survival curve stratified by procedure type is shown in supplementary Figure 1, http://links.lww.com/SLA/B331.

Matched Cohort

Of all MIDPs, 96% could be matched successfully to an ODP control. As shown in Table 1 (matched cohort), significant differences in baseline characteristics were no longer present after matching. Table 2 (matched cohort) shows intraoperative outcomes. Conversion from MIDP to ODP occurred in 62 patients (19%). Median blood loss was lower during MIDP [200 (60–400) vs 300 (150–500) mL, $P = 0.001$]. Splenectomy (93% vs 97%, $P = 0.01$), resection of Gerota's fascia (31% vs 60% patients, $P < 0.001$), and vascular resections (6% vs 11%, $P = 0.012$) were performed less frequently during MIDP compared with ODP. An adrenal gland resection was more often performed during MIDP (11% vs 6%, $P = 0.029$). Table 3 (matched cohort) shows that the median lymph node retrieval was less during MIDP [14 (8–22) vs 22 (14–31) nodes, $P < 0.001$], the lymph node ratio was comparable between both groups [0.06 (0–0.18) vs 0.08 (0–0.17), $P = 0.403$], whereas the R0 resection rate was higher in the MIDP group (67% vs 58%, $P = 0.019$). Lymphovascular invasion (56% vs 71% patients, $P < 0.001$) and perineural tumor invasion (63% vs 75% patients, $P < 0.001$) were

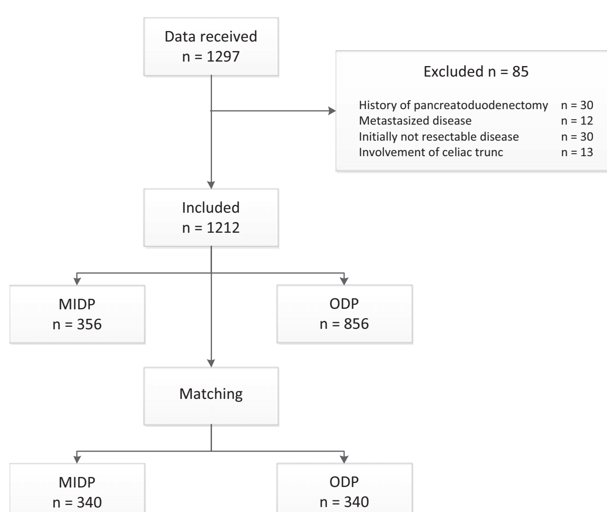
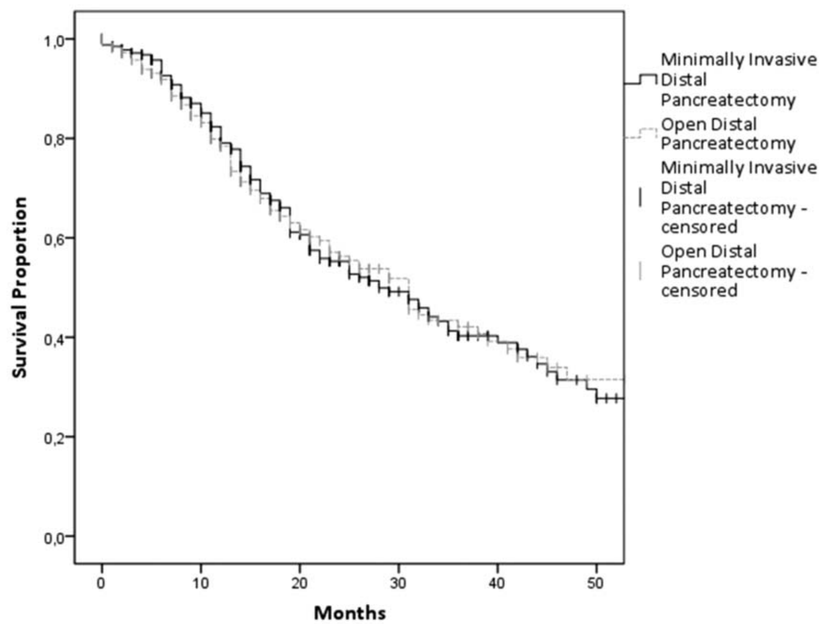


FIGURE 1. Flow-chart.



Number at risk						
MIDP	340	224	118	64	30	16
ODP	340	184	92	50	25	12

FIGURE 2. Kaplan-Meier overall survival matched cohort. Stratified Log-Rank test, $P = 0.774$. Cox proportional hazards model with shared frailty, $P = 0.85$.

TABLE 1. Baseline Characteristics

	Total Cohort			Propensity Score matched Cohort*		
Characteristic	**MIDP (n = 356)**	**ODP (n = 856)**	***P***	**MIDP (n = 340)**	**ODP (n = 340)**	***P***
Female, n (%)	170 (48)	431 (50)	0.410	164 (48)	157 (46)	0.646
Unknown	—	—		—	—	
Age, y, mean (SD)	68 (10)	68 (10)	0.752	68 (10)	68 (10)	0.851
Unknown, n (%)	—	1 (0)		—	—	
BMI, kg/m^2, median (IQR)	25 (23–28)	25 (22–28)	0.446	25 (23–28)	25 (22–28)	0.800
Unknown	65 (18)	116 (14)		—	—	
Previous abdominal surgery, n (%)	92 (34)	293 (40)	0.066	124 (36)	135 (40)	0.396
Unknown	83 (23)	124 (14)		—	—	
ASA physical status, n (%)			0.418			0.497
1	29 (8)	58 (7)		29 (9)	32 (9)	
2	216 (63)	487 (62)		211 (62)	216 (64)	
3	97 (28)	230 (29)		97 (29)	88 (26)	
4	1 (0)	10 (1)		3 (1)	4 (1)	
Unknown	13 (4)	71 (8)		—	—	
Tumor location, n (%)			0.05			0.097
Body	150 (51)	451 (57)		178 (52)	188 (55)	
Body-tail junction	17 (6)	59 (7)		22 (6)	26 (9)	
Tail	127 (43)	279 (35)		140 (41)	143 (42)	
Unknown	62 (17)	67 (8)		—	—	
Tumor size on imaging, mm, median (IQR)	30 (21–40)	30 (21–41)	0.060	30 (21–40)	30 (20–40)	0.250
Unknown	91 (26)	188 (22)		—	—	
Involvement of other organs on imaging, n (%)	17 (6)	108 (13)	0.001	26 (8%)	28 (8%)	0.871
Unknown	79 (22)	44 (5)		—	—	
Neoadjuvant therapy, n (%)						
Chemotherapy	10 (3)	88 (11)	<0.001	11 (3)	18 (5)	0.143
Unknown	5 (1)	19 (2)		—	—	
Radiotherapy	4 (0)	16 (2)	0.352	4 (1)	7 (2)	0.549
Unknown	7 (2)	18 (2)		—	—	

*In the matched cohort, we have no unknown baseline data because of imputation as described in the Methods section.

ASA indicates American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy; SD, standard deviation.

TABLE 2. Operative Outcomes

Outcome	Total Cohort MIDP (n = 356)	Total Cohort ODP (n = 856)	P	Propensity Score matched Cohort* MIDP (n = 340)	Propensity Score matched Cohort* ODP (n = 340)	P
Robot-assisted DP, n (%)	16 (4)	—		16 (5)	—	—
Conversion, n (%)	65 (18)	—	—	62 (19)	–	—
Because of bleeding	17 (26)	—		17 (27)		
Tumor advancement	15 (23)	—		13 (21)		
Vascular involvement	17 (26)	—		16 (26)		
Insufficient overview	4 (6)	—		4 (6)	–	
Technical reason	3 (5)	—		3 (5)		
Adhesions	1 (2)	—		1 (2)		
Unknown	8 (12)	—		8 (13)		
Operative time, min, median (IQR)	239 (180–290)	240 (182–297)	0.520	240 (180–295)	230 (178–286)	0.626
Unknown	14 (4)	27 (3)		23 (7)	23 (7)	
Intraoperative blood loss, mL, median (IQR)	200 (50–400)	300 (150–600)	<0.001	200 (60–400)	300 (150–500)	0.001
Unknown	74 (21)	336 (39)		160 (47)	160 (47)	
Splenectomy, n (%)	328 (92)	828 (97)	<0.001	315 (93)	331 (97)	0.010
Unknown	—	1 (0)		—	—	
Gerota's fascia resection, n (%)	77 (30)	289 (41)	0.002	66 (31)	129 (60)	<0.001
Unknown	96 (27)	146 (17)		124 (36)	124 (36)	
Adrenal gland resection, n (%)	33 (11)	65 (8)	0.165	29 (11)	15 (6)	0.029
Unknown	51 (14)	31 (4)		71 (21)	71 (21)	
Additional organ resection†, n (%)	41 (12)	133 (16)	0.120	33 (11)	35 (12)	0.901
Unknown	27 (8)	29 (3)		52 (15)	52 (15)	
Cholecystectomy	4	16		3	1	
Nephrectomy (partial)	6	14		5	5	
Colectomy (partial)	14	44		10	14	
Small bowel (partial)	7	21		6	3	
Gastrectomy (partial)	10	63		10	17	
Unknown	2	2		2	1	
Vascular resection‡, n (%)	19 (5)	92 (11)	0.003	19 (6)	38 (11)	0.012
Postomesenteric vein	12 (63)	78 (85)		12 (53)	34 (68)	

*Owing to the use of paired tests, analyses could only be performed on data of complete pairs.
†Procedure with additional organ resection besides DP, splenectomy, or adrenalectomy. In some procedures, multiple organ resections were performed.
‡Procedure with additional vascular resection besides splenic vessels.
DP indicates distal pancreatectomy; IQR, interquartile range; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy.

less often seen in the MIDP group. No statistical significant differences in postoperative complications between MIDP and ODP were seen (Table 4, matched cohort). MIDP was associated with shorter postoperative hospital stay compared with ODP [8 (6–12) vs 9 (7–14) days, $P < 0.001$]. The median follow-up time was 13 (range: 0–84) months. Median overall survival was comparable for both procedures {28 [95% confidence interval (CI), 22–34] vs 31 [95% CI, 26–36] months, $P = 0.774$} The hazard ratio was 1.025 (95% CI, 0.75–1.27) for MIDP compared with ODP (P=0.85) (Figure 2).

Sensitivity Analyses

No difference in pathology outcomes and survival was seen after excluding patients who received neoadjuvant therapy (Supplementary Table 1, http://links.lww.com/SLA/B331). Excluding patients after DP without splenectomy did not alter radicality and survival outcome (Supplementary Table 2, http://links.lww.com/SLA/B331), whereas the differences in number of retrieved lymph nodes remained [MIDP 14 (8–22) vs ODP 22 (15–31), $P < 0.001$].

Effect of Time

The matched cohort was divided in 3 different time periods (2006–2011, 2012–2013, and 2014–2015) leaving 3 subgroups with a comparable number of MIDP and ODP patients (Supplementary Table 3, http://links.lww.com/SLA/B331). Results show an increase in robot-assisted procedures (3%–7%) and an increase in the number of splenectomies in the MIDP group (88%–93%). The number of conversions did not differ between time periods. Number of Gerota's fascia resections increased from 18% to 30% and number of vascular resection's from 3% to 12% in the MIDP group. No clear differences in surgical technique and pathology outcomes in the ODP group were seen.

DISCUSSION

This large pan-European retrospective propensity score-matched cohort study on MIDP versus ODP for PDAC confirms short-term clinical advantages of MIDP, more specifically in terms of less intraoperative blood loss and shorter postoperative hospital stay. Overall survival was comparable after both procedures. However, the oncological safety of MIDP for PDAC remains unclear, as despite higher R0 resection rates, Gerota's fascia was resected less often and lymph node retrieval was lower in MIDP. Propensity score matching did not influence these results, but this does not completely exclude the presence of treatment allocation bias.

Three matched cohorts specifically focusing on MIDP versus ODP for patients with PDAC have been published. One study in 102 patients used propensity score matching[25] and 2 studies in 51 and 93 patients used case matching.[26,27] Reduced length of hospital stay after MIDP was reported in 2 studies[25,27] and less intraoperative

TABLE 3. Pathology

Characteristic	Total Cohort MIDP (n = 356)	Total Cohort ODP (n = 856)	P	Propensity Score matched cohort* MIDP (n = 340)	Propensity Score matched cohort* ODP (n = 340)	P
Tumor size, mm, median (IQR)	34 (25–45)	34 (23–47)	0.690	35 (25–45)	30 (23–45)	0.970
Unknown	10 (3)	41 (5)		23 (7)	23 (7)	
Tumor stage			0.100			0.917
T1	24 (7)	75 (9)		22 (7)	27 (8)	
T2	58 (17)	100 (12)		54 (16)	46 (14)	
T3	257 (74)	597 (74)		242 (74)	239 (73)	
T4	10 (3)	37 (5)		10 (3)	16 (5)	
Unknown	7 (2)	47 (5)		12 (4)	12 (4)	
Lymph node stage			0.012			0.007
N0	153 (44)	296 (36)		147 (44)	112 (34)	
N1	198 (56)	530 (64)		184 (56)	219 (66)	
Unknown	5 (1)	30 (4)		9 (3)	9 (3)	
Lymph nodes retrieved, median (IQR)	14 (8–22)	18 (11–28)	<0.001	14 (8–22)	22 (14–31)	<0.001
Tumor positive lymph nodes, median (IQR)	1 (0–2)	1 (0–3)	<0.001	1 (0–2)	2 (0–4)	<0.001
Lymph node ratio, median (IQR)	0.06 (0–0.18)	0,07 (0–0.17)	0.137	0.06 (0–0.18)	0.08 (0–0.17)	0.403
Unknown	6 (2)	23 (3)		9 (3)	5 (1)	
R0 resection†, n (%)	235 (67)	501 (60)	0.015	218 (67)	188 (58)	0.019
Unknown	7 (2)	18 (2)		14 (4)	14 (4)	
Lymphovascular invasion, n (%)	183 (56)	508 (65)	0.002	164 (56)	210 (71)	<0.001
Unknown	28 (8)	80 (9)		46 (14)	46 (14)	
Perineural invasion, n (%)	236 (72)	648 (82)	<0.001	214 (63)	255 (75)	<0.001
Unknown	28 (8)	62 (7)		43 (13)	43 (13)	

*Owing to the use of paired tests, analyses could only be performed on data of complete pairs.
†Defined as a microscopic radical resection with a distance between the tumor and the margin of ≥1 mm.
IQR indicates interquartile range; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy.

blood loss in 1 study[27]. As in the current study, none of the previously published studies reported a difference in postoperative complication rates. Conversion rate was reported in 2 studies and was slightly lower than reported in the present study [12%–17% vs 19% (current study, Table 2].[26,27] This slightly higher rate of conversions could possibly be explained by the inclusion of procedures performed during the learning curve. Owing to a different moment of introduction of MIDP in the participating centers, a decrease in conversion rate over time was not seen (Supplementary Table 3, http://links.lww.com/SLA/B331).

TABLE 4. Postoperative Outcomes

Characteristic	Complete Cohort MIDP (n = 356)	Complete Cohort ODP (n = 856)	P	Propensity Score matched Cohort‡ MIDP (n = 340)	Propensity Score matched Cohort‡ ODP (n = 340)	P
Clavien-Dindo score ≥3 complications, n (%)	62 (17)	186 (22)	0.088	61 (18)	70 (21)	0.431
Unknown	0 (0)	1 (0)		0 (0)	0 (0)	
POPF grade B/C*, n (%)	67 (19)	163 (19)	0.931	65 (19)	67 (20)	0.921
Unknown	1 (0)	2 (0)		1 (0)	1 (0)	
DGE grade B/C†, n (%)	8 (2)	62 (7)	0.002	8 (3)	17 (5)	0.108
Unknown	33 (9)	18 (2)		30 (9)	30 (9)	
PPH grade B/C†, n (%)	15 (5)	29 (3)	0.365	15 (5)	16 (5)	>0.999
Unknown	29 (8)	18 (2)		26 (8)	26 (8)	
Surgical site infection, n (%)	4 (1)	34 (4)	0.022	4 (1)	9 (3)	0.267
Unknown	50 (14)	18 (2)		46 (14)	46 (14)	
Length of hospital stay, d, median (IQR)	8 (5–12)	9 (7–14)	<0.001	8 (6–12)	9 (7–14)	<0.001
Unknown	3 (1)	13 (2)		7 (2)	7 (2)	
Readmission, n (%)	41 (13)	113 (14)	0.580	38 (13)	41 (14)	0.804
Unknown	36 (10)	53 (6)		44 (13)	44 (13)	
90-day mortality, n (%)	8 (2)	28 (4)	0.256	7 (2)	8 (3)	>0.999
Unknown	7 (2)	73 (9)		41 (12)	41 (12)	
Adjuvant chemotherapy, n (%)	226 (74)	482 (73)	0.700	165 (76)	159 (73)	0.561
Unknown	51 (14)	195 (23)		122 (36)	122 (36)	
Time until start adjuvant chemotherapy, d, median (IQR)	54 (41–69)	57 (43–71)		54 (41–67)	57 (45–69)	0.778
Unknown	118 (52)	262 (54)		315 (93)	315 (93)	

*According to the International Study Group on Pancreatic Fistula definition.
†According to the International Study Group on Pancreatic Surgery definition.
‡Owing to the use of paired tests, analyses could only be performed on data of complete pairs.
IQR indicates interquartile range.

The 3 previous matched cohorts did not report significant differences in R0 resection rates, although the absolute risk difference between MIDP and ODP did favour MIDP in all cohorts and ranged from 8% to 9%, similar to the 9% found in our study (Table 3, matched cohort).[26,27] It should be noted that comparisons of R0 resection rates in the literature have to be considered with caution, as R0 rates are influenced by the definition used (no involvement of the margin or a distance between the margin and the tumor of at least 1 mm) and method of margin assessment (transection margin alone or also circumferential margins) which, in absence of standardized pathology assessment and reporting, may vary per pathologist and per institution. A systematic review illustrated this problem as it reported R0 margin rates in large randomized controlled trials for resected PDAC as ranging from 17% to 100%.[28]

In contrast to previously reported matched cohorts, the present study did show a significantly lower lymph node retrieval (14 vs 22, $P < 0.001$) with MIDP (Table 3, matched cohort), which was not related to the lower amount of splenectomies in this group (supplementary table 2, http://links.lww.com/SLA/B331). The amount of retrieved lymph nodes depends on the extent of the lymphadenectomy performed. The ISGPS definition of a standard lymphadenectomy[29] recommends removal of lymph node station 10, 11, and 18 for body and tail tumors and additional removal of station 9 is suggested in case of tumors confined to the area of the body of the pancreas. However, data on the type of lymphadenectomy performed were not available in this study and as no evidence on the number of lymph nodes that should be resected is available, the clinical relevance of our finding remains uncertain.

The concerns on the oncological safety of MIDP for PDAC could be related to worries about the ability to perform a R0 resection or adequate lymphadenectomy. It is therefore interesting to assess the details of surgical technique, resection of Gerota's fascia, and left adrenal gland resection, which are suggested to be relevant in achieving a R0 resection and adequate lymphadenectomy.[30–32] Standardized techniques have been described for MIDP in PDAC,[31] following the RAMPS technique as described by Strasberg.[30,32] MIDP for PDAC should include standardized lymphadenectomy, resection of Gerota's fascia to reduce the risk of incomplete resection on the posterior margin as well as a ''no-touch approach'', by lifting the pancreas using a hanging maneuver.[31] This approach permits good views and access to the posterior aspect of the pancreas allowing for resection of Gerota's fascia and the adrenal gland, if needed. Both in the total and the matched cohort, we found resection of Gerota's fascia and splenectomy to be less often performed in the MIDP group (Table 2). Adrenal gland resection, however, was surprisingly performed more often in the MIDP group compared with ODP. The previous mentioned standardized surgical techniques in DP were introduced parallel to the introduction of MIDP and this could have caused the differences in surgical technique used between MIDP and ODP. The subgroup analyses on effect of time only showed an increase in Gerota's fascia resection in the MIDP group (18% to 30%) and therefore do not explain the differences in surgical technique between both groups (Supplementary table 3, http://links.lww.com/SLA/B331). It remains unclear whether the differences found were related to the incapability to perform these steps minimally invasive or open or, whether surgeons did not consider these required for the cancers they resected, indicating that, despite matching, different tumors were present in the MIDP group.

No significant differences in overall survival have been reported for MIDP versus ODP in PDAC[25–27] and overall survival ranged from 14 to 16 months.[26,27] Although the present study neither found a significant difference in survival between groups, the reported survival was overall higher, ranging from 29 (MIDP) to 31 (ODP) months (Table 4, matched cohort). However, several large nonmatched studies have reported survival times comparable to our study but definitions of PDAC did differ.[25,33]

Despite the clear strengths of this study, some limitations have to be discussed. First, most data were collected retrospectively, which could have possibly led to underreporting of postoperative outcomes such as complications. Second, missing data were present. However, no differences between the baseline characteristics before and after imputation were present (Supplementary Table 1, http://links.lww.com/SLA/B331). For optimal transparency, all missing variables were reported and data should be interpreted in perspective to the degree of missing data. Third, despite our attempt to minimize the influence of treatment allocation bias, by applying propensity score matching, treatment allocation bias may still have influenced outcomes in the matched cohort. Although we managed to correct for differences in baseline variables, the difference in lymphovascular and perineural tumor invasion between the MIDP and ODP group (Table 3, matched cohort) suggests that less aggressive tumors have been selected for the minimally invasive approach. However, lymph node ratio was comparable between both groups. Perineural invasion has only been reported in a single small matched cohort study, and in contrast to the present study, no statistical significant difference between MIDP and ODP was seen.[27] Previous matched studies did not report on lymphovascular tumor invasion. The presence of perineural and lymphovascular tumor invasion is associated with worse survival in the literature,[26,34] and differences between MIDP and ODP could therefore influence outcomes and should be reported in all studies assessing this subject. Fourth, this study was mainly a European effort and a median BMI of 25 was reported, which is lower compared to, for example, the median BMI in the United States. Consequently, this difference could influence the applicability of the results of the current studies to non-European countries. Attempts should be made to include centers from outside of Europe in further studies. Lastly, the possible variation in surgical techniques and pathology assessment and reporting between centers represent a serious challenge. The influence of these variations on the results remains unknown and could be limited because of the use of the same approach in MIDP and ODP at a given center. Efforts to develop standardized surgical technique, pathology assessment, and pathology reporting should be made and the influence of implementation of these guidelines should be studied.

The results of the present study show that the oncological safety of MIDP remains uncertain. Standardization and agreement with regards to intraoperative techniques (lymphadenectomy, adrenal gland, Gerota's fascia resection, and splenectomy) are required to be able to further investigate this subject. The E-MIPS group is currently preparing for the DIPLOMA-trial (Distal Pancreatectomy, Minimally Invasive or Open for PDAC; www.e-mips.org), which will further investigate the oncologic non-inferiority (radicality, survival) of MIDP to ODP for PDAC in a multicenter randomized setting with standardized surgical technique and pathology assessment and reporting.

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