Minimally invasive versus open distal pancreatectomy for ductal adenocarcinoma (DIPLOMA): a pan-European propensity score matched study

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Mini-abstract (42/50)

Data on oncological safety of minimally invasive distal pancreatectomy (MIDP) for pancreatic ductal adenocarcinoma (PDAC) are scarce. This pan-European propensity score matched study found higher R0-resection rates, lower lymph node retrieval and comparable survival after MIDP vs. open distal pancreatectomy for PDAC.

Structured Abstract (250/250 words)

Objective: To compare oncological outcomes after minimally invasive distal pancreatectomy (MIDP) vs. open distal pancreatectomy (ODP) in patients with pancreatic ductal adenocarcinoma (PDAC).

Summery Background Data: Cohort studies have suggested superior short-term outcomes of MIDP compared with ODP. Recent international surveys, however, revealed that surgeons have concerns about the oncological safety of MIDP for PDAC.

Methods: A pan-European propensity score matched (PSM) study including patients who underwent MIDP or ODP for PDAC between January 1st, 2007 and July 1st, 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. Out of 356(29%) MIDP patients, 340 could be matched to an ODP control. After matching, the MIDP conversion rate was 19%(n=62). Median blood loss (200mL[60–400] vs. 300mL[150–500], *P*=0.001) and hospital stay (8[6-12] vs. 9[7-14] days, *P*<0.001) were less after MIDP. Clavien-Dindo grade ≥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 rate (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 vs. 31 months (*P*=0.929).

Conclusion: Although survival did not differ between MIDP and ODP for PDAC, the opposing differences in R0 resection rate, resection of Gerota's fascia and lymph node retrieval require confirmation of the oncological safety of MIDP in a randomized trial.

Introduction

Minimally invasive distal pancreatectomy (MIDP), defined as either laparoscopic or robot-assisted distal pancreatectomy, was introduced in 1994.[1] Several systematic reviews of cohort studies have suggested superior short-term outcomes of MIDP 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 non-radical (R1/R2) resection margins, tumor recurrence, and survival after MIDP and ODP.[12] Importantly, as randomized controlled trials were lacking most studies were single-center and retrospective, leading to concerns on the impact of treatment allocation bias. Further concerns on the oncological outcomes of MIDP for patients with PDAC were raised in two 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 contra-indication for a minimally invasive aproach[14]. Surgeons may doubt whether the essential components of an adequate oncological resection during distal pancreatectomy (i.e. radical resection margins, resection of Gerota's fascia, splenectomy 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) in order to safely implement minimally invasive pancreatic surgery. This group designed the DIPLOMA project (Distal Pancreatectomy, minimally invasive or open for

malignancy), 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 due to the observational study design.

Design and patients

This pan-European retrospective cohort study was performed within centers of the E-MIPS. All consecutive patients who underwent distal pancreatectomy (minimally invasive or open) with a histopathological diagnosis of PDAC between January 1st, 2007 and July 1st, 2015 were eligible for inclusion. Patients were excluded if they had a previous pancreatic resection, if distant metastasis were present, if the tumor involved the celiac trunc or when the tumor only became resectable after down staging with neo-adjuvant 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[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 3 or higher. 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 considered clinically relevant and subsequently registered. Surgical site infection (SSI) was defined using the Centers for Disease Control and Prevention (CDC) definition.[21] Resection margins, including transection and circumferential margins, were categorized into; R0 (distance margin to tumor ≥1mm), R1 (distance margin to tumor <1mm) and R2 (macroscopically positive margin) according to the Royal College of Pathologists definition.[22]

Data collection

All 34 participating centers received a blank database including all parameters of interest. The data were collected locally by each participating center and combined centrally by the study coordinators. The participating centers received a survey regarding the method of local data collection (e.g. 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, tumor location, tumor size (mm) and tumor involvement of other organs on pre-operative imaging and administration of neoadjuvant therapy. Collected outcomes were procedure type (open, minimally invasive), conversion and reason for conversion, operative time (min.), 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, re-admissions 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 scores for the intervention group (MIDP as primary treatment). Baseline variables available (age, sex, BMI, ASA physical status, prior abdominal surgery, neoadjuvant therapy, year of surgery and tumor size, involvement of other organs and tumor location on preoperative imaging) were included.

Nearest neighbor matching was performed in a 1:1 ratio without replacement and a caliper width of 0.01 was specified. In order to be able to calculate propensity scores for all patients, missing baseline variables were imputed using single imputation based on predictive mean matching.

Statistical analysis

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. Normally distributed continuous data are presented as means with standard deviations (SDs) and were compared using the two independent samples t-test. Non-normally distributed continuous data are presented as medians with interquartile ranges (IQRs) 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's 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] A p-value below 0.05 was considered statistically significant.

Results

Participating centers

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 MIDPs [10-26] per year.

Total cohort

In total, 1297 patients were identified, 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%) 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*≤0.001). Intra-operative 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*≤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.

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 intra-operative outcomes. Conversion from MIDP to ODP occurred in 62 patients (19%). Median blood loss was lower during MIDP compared with ODP (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 compared with ODP (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) 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 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% CI 22 – 34] vs. 31 [95% CI 26 – 36] months, *P*=0.774) The Hazard Ratio, determined with a Cox proportional hazard regression with shared frailty analysis was 1.025 (95% CI 0.75 – 1.27) for MIDP compared with ODP (*P* = 0.85).

Discussion

This large pan-European retrospective propensity score matched cohort study on MIDP vs. 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 but the oncological safety of MIDP for PDAC, however, remains unclear as R0 resection rate was higher but, Gerota's fascia was resected less often and lymph node retrieval was lower in MIDP. Matching did not influence these results, but, this does not exclude the presence of treatment allocation bias.

Three other matched cohorts specifically focusing on MIDP vs. ODP for patients with PDAC were published, one study in 102 patients used propensity score matching[25] and two studies in 51 and 93 patients which used case matching.[26,27] Reduced length of hospital stay after MIDP was reported in two studies[25,27] and less intraoperative blood loss in one study[27]. As in the current study, none of the previously published studies reported a difference in postoperative complication rates.

The three 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%, which is 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 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]

The number of retrieved lymph nodes also did not differ significantly in the previous matched cohorts, whereas in the current study we did find that a median of 8 less lymph nodes were retrieved during MIDP (Table 3, matched cohort). The amount of retrieved lymph nodes depends on the extend 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. 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 was not available in this study, and since no evidence on the number of lymph nodes that should be resected is available the clinical relevance of our finding remains uncertain.

It is interesting to assess at details of surgical technique for instance, splenectomy, resection of Gerota's fascia and left adrenal gland resection, which are suggested to be relevant in achieving an R0 resection and adequate lymphadenectomy.[30-32] Both in the total and the matched cohort we found splenectomy and resection of Gerota's fascia to be less often performed in the MIDP group (Table 2). Adrenal gland resection on the other hand, was surprisingly performed more often in the MIDP group compared with ODP. It is 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.

The concerns on the oncological safety of MIPD for PDAC, could be related to worries about the ability to perform a R0 resection or adequate lymphadenectomy. Standardized techniques have been described for MIDP in PDAC[31], following the RAMPS technique as described by Strassberg[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. 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.

Therefore, with proper patient selection differences in R0 resection rate, lymph node retrieval and, Gerota and adrenal gland resection should not be a concern in experienced hands.

No significant differences in overall survival have been reported for MIDP vs. ODP in PDAC[25-27] and overall survival ranged from 14 to 16 months[26,27]. Although the current study neither found a significant difference in survival between groups, the reported survival was overall higher, ranging from 29 (MIDP) and 31 (ODP) months (Table 4, matched cohort). On the other hand, several large non-matched studies have reported survival times comparable to our study.[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). For optimal transparency, all missing variables were reported and data should be interpreted in perspective to them. Third, despite our attempt to minimize the influence of treatment allocation bias, by applying PSM, 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. The absence of these factors are associated with better survival in the literature,[26,34] and as a consequence, this could influence the results. Lastly, the variation in techniques, reflected in the inclusion and sparing of the Gerota's fascia by different surgeons and in different centers, the lack of information on the location of lymph nodes resected represent a serious challenge to the comparison of homogenous groups

Due to the unknown clinical relevance of these findings in the present study, the oncological safety of MIDP remains uncertain. Standardization and agreement with regards to intraoperative

techniques (splenectomy, lymphadenectomy, adrenal gland and Gerota's fascia resection) is required in order 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) which will further investigate non-inferiority of MIDP vs. ODP for PDAC in a multicenter randomized setting. Such a study should include standardized surgical technique (e.g. regarding splenectomy, Gerota's fascia and lymphadenectomy) and standardized pathology assessment and reporting.

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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 (61 – 74)	68 (61 – 75)	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)	9 (26)	
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)		-	-	

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.

*In the matched cohort we have no unknown baseline data due to imputation as described in the methods section.

TABLE 2. Operative outcomes

	Total Cohort			*Propensity Score Matched cohort**		
Outcome	**MIDP (n = 356)**	**ODP (n = 856)**	***P***	**MIDP (n = 340)**	**ODP (n = 340)**	***P***
Robot-assisted DP, n (%)	16 (4)	-		16 (5)	-	-
Unknown	-			-		
Conversion, n (%)	65 (18)	-	-	62 (19)	-	-
Unknown	-	-		-		
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
Unknown	-	-		-	-	
Postomesenteric vein	12 (63)	78 (85)		12 (53)	34 (68)	

DP indicates distal pancreatectomy; IQR, interquartile range; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy.

*Due 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.

TABLE 3. Pathology

	Total Cohort			*Propensity Score Matched cohort**		
Characteristic	**MIDP (n = 356)**	**ODP (n = 856)**	***P***	**MIDP (n = 340)**	**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
Unknown	11 (3)	10 (1)		15 (4)	15 (4)	
Tumor positive lymph nodes retrieved, median (IQR)	1 (0 – 2)	1 (0 – 3)	< 0.001	1 (0 – 2)	2 (0 – 4)	< 0.001
Unknown	5 (1)	21 (2)		9 (3)	9 (3)	
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)	

IQR indicates interquartile range; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy.

*Due 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

TABLE 4. Postoperative outcomes

	Complete Cohort			*Propensity Score Matched cohort*		
Characteristic	**MIDP (n = 356)**	**ODP (n = 856)**	***P***	**MIDP (n = 340)**	**ODP (n = 340)**	***p***
Clavien-Dindo score ≥ III 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)	

IQR, interquartile range; MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy.

*According to the International Study Group on Pancreatic Fistula definition

** According to the International Study Group on Pancreatic Surgery definition

Figure 1: Flow diagram

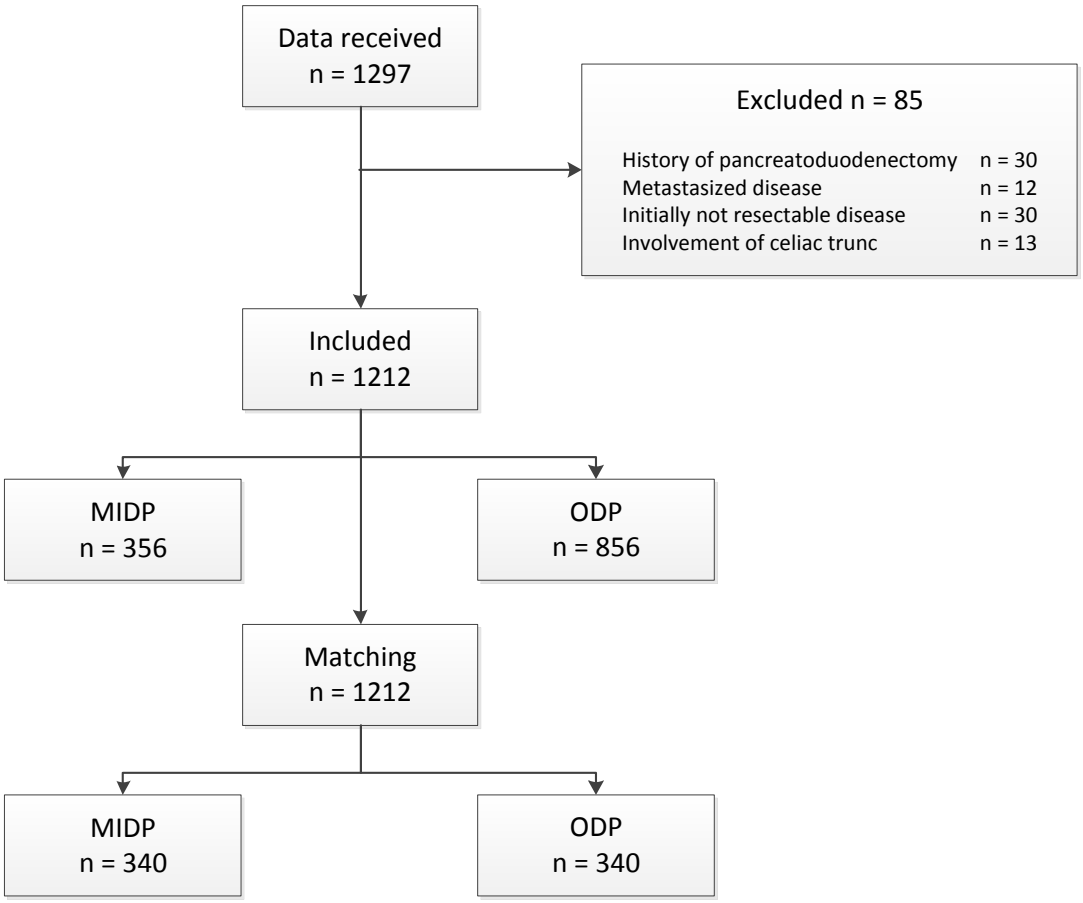
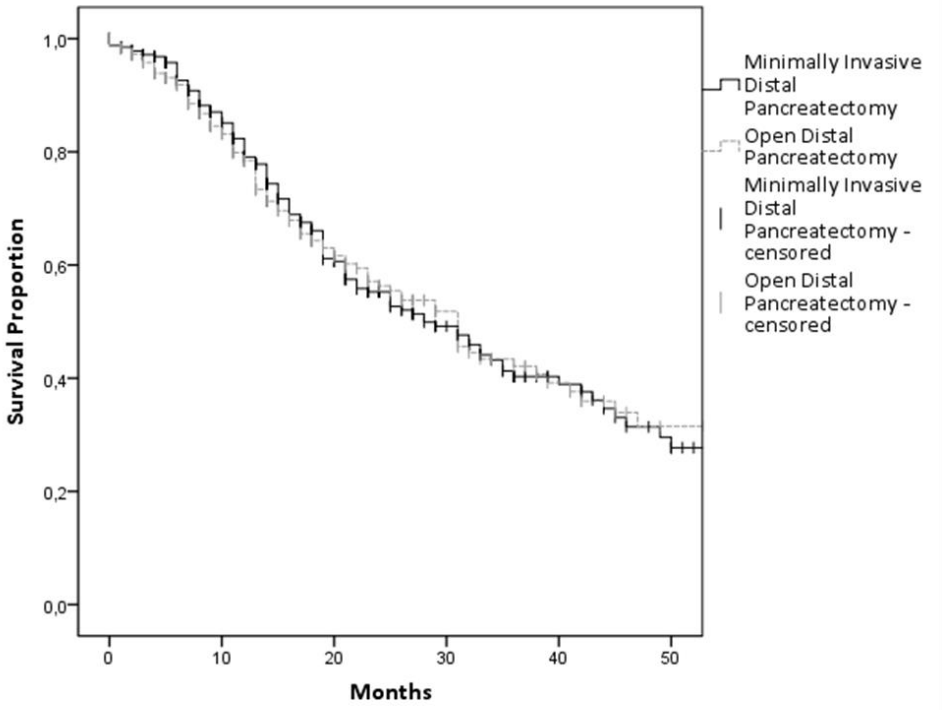


Figure 2: Kaplan-Meier overall survival matched cohort. Stratified Log-Rank test, *P* = 0.774. Cox proportional hazards model with shared frailty, *P* = 0.85



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

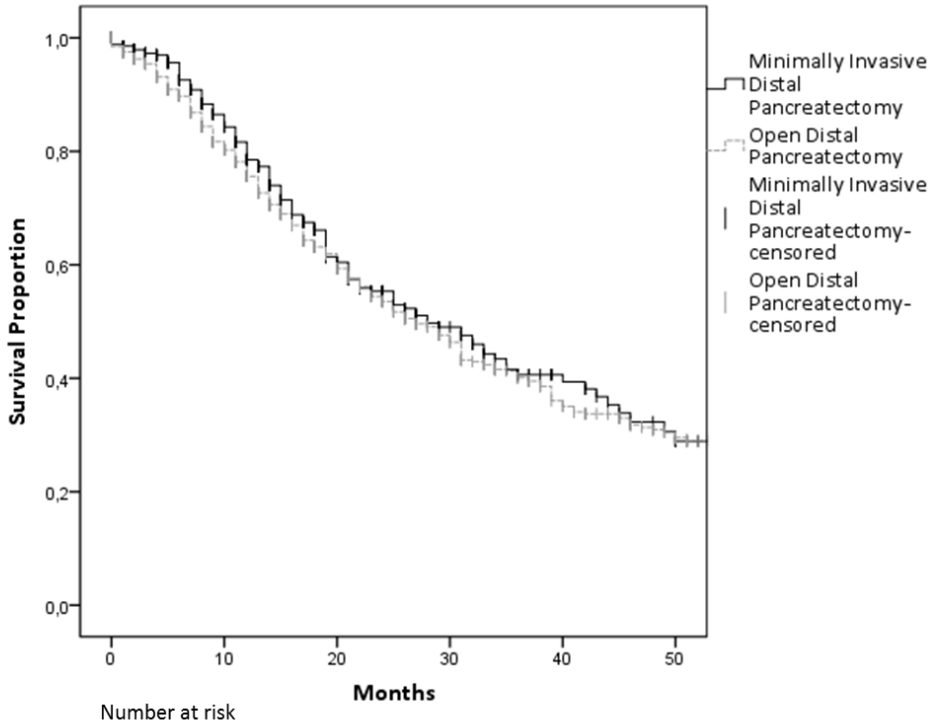
Supplementary table 1. Baseline characteristics after imputation

	Complete Cohort			*Complete Cohort after imputation*		
Characteristic	**MIDP (n = 356)**	**ODP (n = 856)**	***P***	**MIDP (n = 356)**	**ODP (n = 856)**	***p***
Female, n (%)	170 (48)	431 (50)	0.410	170 (48)	431 (50)	0.410
Unknown	-	-		-	-	
Age, y, mean (SD)	68 (61 – 74)	68 (61 – 75)	0.752	67 (10)	67 (10)	0.772
Unknown, n (%)	-	1 (0)		-	-	
BMI, kg/m^2, median (IQR)	25 (23 – 28)	25 (22 – 28)	0.446	25 (22 – 28)	25 (22 – 28)	0.400
Unknown	65 (18)	116 (14)		-	-	
Previous abdominal surgery, n (%)	92 (34)	293 (40)	0.066	116 (33)	342 (40)	0.016
Unknown	83 (23)	124 (14)		-	-	
ASA physical status, n (%)			0.418			0.124
1	29 (8)	58 (7)		30 (8)	62 (7)	
2	216 (63)	487 (62)		226 (64)	520 (61)	
3	97 (28)	230 (29)		99 (28)	258 (30)	
4	1 (0)	10 (1)		1 (0)	16 (2)	
Unknown	13 (4)	71 (8)		-	-	
Tumor location, n (%)			0.05			0.117
Body	150 (51)	451 (57)		183 (51)	486 (57)	
Body-tail junction	17 (6)	59 (7)		22(6)	61 (7)	
Tail	127 (43)	279 (35)		151 (42)	309 (36)	
Unknown	62 (17)	67 (8)		-	-	
Tumor size on imaging, mm, median (IQR)	30 (21 – 40)	30 (21 – 41)	0.060	30 (20 – 40)	30 (21 – 40)	0.054
Unknown	91 (26)	188 (22)		-	-	
Involvement of other organs on imaging, n (%)	17 (6)	108 (13)	0.001	28 (10%)	120 (15%)	0.050
Unknown	79 (22)	44 (5)		-	-	
Neoadjuvant therapy, n (%)						
Chemotherapy	10 (3)	88 (11)	<0.001	10 (3)	88 (11)	<0.001

Unknown	5 (1)	19 (2)		-	-	
Radiotherapy	4 (0)	16 (2)	0.352	4 (1)	16 (2)	0.352
Unknown	7 (2)	18 (2)		-	-	

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.

Supplementary figure 1: Kaplan-Meier overall survival total cohort. Log-Rank test, *P* = 0.371.



Number at risk						
MIDP	340	232	125	68	32	18
ODP	340	509	307	186	112	65