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European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS); Korrel, Maarten; Jones, Leia R.; van Hilst, Jony; Balzano, Gianpaolo; Björnsson, Bergthor; Boggi, Ugo; Bratlie, Svein Olav; Busch, Olivier R.; Butturini, Giovanni

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Minimally invasive versus open distal pancreatectomy for resectable pancreatic cancer (DIPLOMA): an international randomised non-inferiority trial



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Summary

Background The oncological safety of minimally invasive surgery has been questioned for several abdominal cancers. Concerns also exist regarding the use of minimally invasive distal pancreatectomy (MIDP) in patients with resectable pancreatic cancer as randomised trials are lacking.

Methods In this international randomised non-inferiority trial, we recruited adults with resectable pancreatic cancer from 35 centres in 12 countries. Patients were randomly assigned to either MIDP (laparoscopic or robotic) or open distal pancreatectomy (ODP). Both patients and pathologists were blinded to the assigned approach. Primary endpoint was radical resection (R0, ≥ 1 mm free margin) in patients who had ultimately undergone resection. Analyses for the primary endpoint were by modified intention-to-treat, excluding patients with missing data on primary endpoint. The pre-defined non-inferiority margin of -7% was compared with the lower limit of the two-

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sided 90% confidence interval (CI) of absolute difference in the primary endpoint. This trial is registered with the ISRCTN registry (ISRCTN44897265).

Findings Between May 8, 2018 and May 7, 2021, 258 patients were randomly assigned to MIDP (131 patients) or ODP (127 patients). Modified intention-to-treat analysis included 114 patients in the MIDP group and 110 patients in the ODP group. An R0 resection occurred in 83 (73%) patients in the MIDP group and in 76 (69%) patients in the ODP group (difference 3.7%, 90% CI -6.2 to 13.6%; $p_{\text{non-inferiority}} = 0.039$). Median lymph node yield was comparable (22.0 [16.0–30.0] vs 23.0 [14.0–32.0] nodes, $p = 0.86$), as was the rate of intraperitoneal recurrence (41% vs 38%, $p = 0.45$). Median follow-up was 23.5 (interquartile range 17.0–30.0) months. Other postoperative outcomes were comparable, including median time to functional recovery (5 [95% CI 4.5–5.5] vs 5 [95% CI 4.7–5.3] days; $p = 0.22$) and overall survival (HR 0.99, 95% CI 0.67–1.46, $p = 0.94$). Serious adverse events were reported in 23 (18%) of 131 patients in the MIDP group vs 28 (22%) of 127 patients in the ODP group.

Interpretation This trial provides evidence on the non-inferiority of MIDP compared to ODP regarding radical resection rates in patients with resectable pancreatic cancer. The present findings support the applicability of minimally invasive surgery in patients with resectable left-sided pancreatic cancer.

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Keywords: Distal pancreatectomy; Pancreatic ductal adenocarcinoma; Minimally invasive surgery

Research in context

Evidence before this study

Prior to the start of our trial, we performed an extensive systematic literature review using PubMed, Embase, and the Cochrane library database on studies published before March 9, 2018. We used search terms including “distal pancreatectomy”, “pancreatic adenocarcinoma”, and “minimally invasive surgery”. We only included comparative studies on minimally invasive vs open distal pancreatectomy for pancreatic cancer, published in English. We identified 21 retrospective cohort studies with a total of 11,246 patients. No randomised controlled trials were identified. Each study had a moderate to high risk of bias and several limitations (including selection bias, small number of patients, retrospective study design). Radical resection rate (odds ratio 1.24) and overall survival rate (hazard ratio 0.86) were comparable between groups, whereas tumor size (weighed mean difference -0.46 cm) and lymph node yield (weighed mean difference -1.3 lymph nodes) were lower in minimally invasive distal pancreatectomy.

Added value of this study

Our study is the first randomised trial to compare minimally invasive distal pancreatectomy with the current standard approach of open distal pancreatectomy in patients with resectable pancreatic cancer. Hence, our study is the first to provide level 1 evidence on the oncological safety and feasibility of minimally invasive distal pancreatectomy in patients with pancreatic cancer.

Implications of all the available evidence

Based on the results of this study, we expect that minimally invasive distal pancreatectomy will be incorporated in guidelines as a standard, valid approach in patients with resectable pancreatic cancer. Oncological outcome is non-inferior to the open approach without any evidence for impaired safety.

Introduction

Pancreatic cancer (i.e., pancreatic ductal adenocarcinoma) is currently the third most lethal cancer worldwide with a five-year survival rate of 5–10%.¹ Mortality rates of pancreatic cancer have increased from 8.6/100,000 persons in 2000 to 9.5/100,000 in 2019.² Patients with left-sided pancreatic cancer represent less than 10% of all patients with resectable pancreatic cancer.³ Distal pancreatectomy (formally ‘left radical

pancreatectomy’) with splenectomy followed by adjuvant chemotherapy is the preferred treatment in these patients, with a five-year survival rate of approximately 20%.^{1,4}

Traditionally, distal pancreatectomy was performed using an open approach. Since its first introduction in 1994,⁵ minimally invasive distal pancreatectomy (MIDP) has been gaining popularity. Several retrospective studies and two randomised trials demonstrated short-

term benefits in terms of functional recovery and hospital stay after MIDP over ODP for all indications.^{6–8} However, concerns remain regarding the oncological safety of MIDP in patients with resectable pancreatic cancer. Those concerns were highlighted by an international survey study wherein one-third of pancreatic surgeons expected inferior oncological outcomes after MIDP for pancreatic cancer.⁹ A systematic review and meta-analysis including over 11,000 patients reported comparable radical resection rates and survival after MIDP and ODP, but a decreased lymph node yield with MIDP.¹⁰ Recently, these concerns regarding the safety of minimally invasive surgery for other abdominal cancers were highlighted by a randomised trial that reported worse survival outcomes after minimally invasive hysterectomy in patients with cervical cancer.¹¹ Results of this randomised trial led to a decreased use of minimally invasive hysterectomy.¹² Additionally, two randomised trials were not able to confirm the non-inferiority of minimally invasive surgery on pathological outcomes in patients with colorectal cancer.^{13,14}

To address these concerns, a pragmatic international randomised trial was designed to investigate the oncological safety of MIDP as compared to ODP in patients with resectable pancreatic cancer in a non-inferior setup.

Methods

Study design and participants

The investigator-initiated international multicentre non-inferiority randomised DIPLOMA trial included patients aged 18 years and older with potentially resectable pancreatic cancer (i.e., ductal adenocarcinoma) of the body and tail. Procedures were performed in 35 high-volume hospitals across 12 countries collaborating in the European Consortium on Minimally Invasive Pancreatic Surgery (www.e-mips.com). Initially, 38 centres were planned to participate, however, three centres were unable to start patient inclusion due to delay in legal approval. To ascertain sufficient surgical experience and quality, each participating surgical team had to perform at least 15 distal pancreatectomies (any diagnosis) annually and should have performed at least 50 MIDPs prior to start of trial enrolment. Similar to current clinical practice, preoperative pathological proof of the diagnosis of pancreatic cancer was not mandatory, except for patients receiving neoadjuvant therapy. Pancreatic cancer was defined according to the World Health Organisation definition, including adenocarcinoma, colloid carcinoma (mucinous non-cystic carcinoma), hepatoid carcinoma, medullary carcinoma, signet ring cell carcinoma, undifferentiated carcinoma and undifferentiated carcinoma with osteoclast-like giant cells.¹⁵ Patients who received neoadjuvant chemotherapy were considered eligible only if

the tumor was upfront resectable. Initially, patients receiving neoadjuvant chemotherapy were excluded, but this was amended in the protocol after the enrolment of the first 11 patients. Patients with multivisceral involvement (i.e., beyond the pancreas and spleen) were considered eligible. Exclusion criteria were American Society of Anaesthesiology physical status >3, distant metastases, and tumor involvement or abutment of major vessels (excluding the splenic vessels),¹⁶ see [Appendix](#) (p 2).

All patients provided written informed consent before randomisation. The study protocol was initially approved by the Amsterdam UMC and Southampton University Hospital ethics committees and thereafter by all individual ethics committees of the participating centres. The study protocol was previously published.¹⁷

This study was performed and reported according to the CONSORT guidelines for randomised controlled trials ([Appendix](#) pp 26–27).

Randomisation and blinding

Patients were randomly assigned to the minimally invasive approach and open approach in a 1:1 ratio. Permuted-block randomisation with varying block sizes (4–6–8) and stratification for hospital volume (≤ 20 , 21–40, >40 distal pancreatectomies annually) and multivisceral involvement was performed by the study coordinators (MK, LJ, FV, SL, AE) centrally in Amsterdam and Southampton initially, and since October 2019 in Amsterdam and Brescia using a web-based randomisation module (Castor EDC, CIWIT B.V., Amsterdam, the Netherlands).

Pathologists and patients were blinded for the assigned treatment group to minimize bias in the assessment of the primary endpoint and functional recovery. For pathologists, the allocated treatment was not disclosed. After skin closure, patients were blinded using a large abdominal dressing (appropriate for the size of the ventral abdomen) which was securely taped to obstruct the view of the abdomen. This dressing was removed on postoperative day 5 or earlier when all five criteria of the functional recovery checklist were met, or for clinical reasons ([Appendix](#) p 3). The efficacy of blinding was assessed by asking the pathologist which surgical approach they believed the patient had received and by asking the patient, prior to removal of the abdominal dressing, which approach they had received.

Procedures

Patients were screened for eligibility in each individual participating centre during a multidisciplinary tumor board meeting. At the time of distal pancreatectomy, an abdominal CT-scan of maximum 4 weeks old was required to minimize the risk of progression to vascular contact or metastases during the waiting period. After randomisation, the trial coordinator contacted the

surgical team prior to surgery with information including quality of life questionnaires, functional recovery checklists, and documents containing surgery and histopathology webinars with standardised procedures.

Surgical procedures were performed according to the left radical pancreatectomy principles, rather than the distal pancreatectomy principles.^{18,19} Left radical pancreatectomy would be the preferred terminology considering the oncological magnitude and currently ongoing change in terminology. To obtain homogeneity in terminology with respect to the published trial protocol, distal pancreatectomy is used in this manuscript.

Standardised surgical and histopathological procedures had been agreed on during several physical central meetings with participating surgeons and pathologists prior to study initiation. Each centre was trained in the protocol during a physical initiation meeting with the trial coordinators prior to the first inclusion and thereafter through online webinars. Previously published surgical standards for oncological resection during distal pancreatectomy were followed: radical antegrade modular pancreateosplenectomy²⁰ for open procedures and radical 'no-touch' left pancreateosplenectomy for minimally invasive procedures.¹⁸ Both surgical procedures included standardised pancreatic transection, standardised lymph node dissection, routine splenectomy with resection of Gerota's (i.e., perirenal) fascia with or without left adrenal gland based on the location of the tumour. Pancreatic transection was performed at the pancreatic neck and preferably performed using stapler devices, but other techniques were allowed as long as these were used in the same manner during ODP and MIDP per centre. The height of the staplers was left to the surgeon's discretion depending on intraoperative assessment of the pancreas. Surgical sutures were placed after specimen extraction at the transection and posterior margin to facilitate pathologist orientation during histopathology assessment. Histopathological procedures were previously published.²¹ This included standardised orientation, inking, fixation, block taking and macroscopic and microscopic assessment. Each pathologist was trained in this standardised pathology protocol prior to the first specimen assessment.

Postoperative care was according to an enhanced recovery protocol.²² Patients received quality of life questionnaires at 2 weeks and 1-, 3-, and 6-months postoperatively. Patients also received a questionnaire for the scar satisfaction score and pain at 12 months postoperatively. These scores ranged from 1 (completely unsatisfied) to 10 (completely satisfied) for scar scores and from 0 (no pain) to 10 (severe pain) for pain scores.

Data collection was performed by local physicians using web-based data collection software (Castor EDC, CIWIT B.V., Amsterdam, the Netherlands).

Outcomes

The primary outcome was radical resection (R0), defined as the minimum margin of ≥ 1 mm between tumor and surgical margin, measured at the transection and posterior margins in patients who underwent a resection (regardless of the ultimate histopathological diagnosis).¹⁹ Predefined secondary outcomes included time to functional recovery, length of hospital stay, overall and pancreas-specific complications, post-operative transfusions, surgical site infections, readmissions, mortality, histopathology outcomes (e.g., lymph node yield, tumor differentiation, and perineural and lymphovascular invasion), overall and disease-free survival, time and site of disease recurrence or progression, and quality of life up to 6 months post-operatively (i.e., generic and disease-specific health status by EQ-5D-5L and QLQ-C30 respectively, and scar satisfaction scores). Morbidity and mortality outcomes were assessed up to 90 days postoperatively. The definitions of outcomes in this trial are reported in the [Appendix](#) (p 3).

A blinded adjudication committee crosschecked the primary and secondary endpoints with the respective definitions. Disagreements were resolved during a plenary consensus meeting. After enrolment of 50, 100, and 258 patients, an independent data monitoring committee assessed patient accrual and safety endpoints including adverse events. Coordinating centres (University Hospital Southampton and Amsterdam UMC) had regular monitoring visits. Monitoring of each participating centre was according to local regulatory protocols.

Statistical analysis

The sample size calculation was based on the results of a previously published observational study of >1300 patients.²³ Including results of this observational study, assuming a non-inferiority margin of -7% for radical resection rates (58% in the ODP group and 67% in the MIDP group), a power of 80% ($1-\beta$) and significance level of 5% (α), the minimum number of patients required was 226. The 7% 'minimally clinically important difference' margin was based on discussion within the larger study group, in the absence of a consensus or data in the literature. Considering an expected dropout rate of 2.5% and 10% rate of patients with occult metastatic disease detected at surgical exploration, we calculated a sample size of 258 patients.

Analyses were by intention-to-treat, unless stated otherwise. Patients who were randomised to MIDP but were converted to ODP were analysed in the MIDP group. Patients who received another procedure than distal pancreatectomy were also analysed in the assigned group. Analyses for the primary endpoint and for the secondary endpoints of histopathology outcomes, post-operative pancreas-specific complications, and functional recovery were by modified intention-to-treat. This

included only patients who had ultimately undergone a resection of their tumour, as these data were not available for patients who did not. Besides, patients who did not undergo a resection were not blinded for allocation for ethical reasons. Patients with other diagnoses than pancreatic cancer, but in whom radicality of resection could be reliably assessed (e.g., neuroendocrine tumours, metastases of different primary tumor), were included in the modified intention-to-treat population. A best- and worst-case analysis was performed for the primary endpoint to correct for missing data; in best-case analysis, those with missing data in the MIDP group were imputed as radical resection (R0) and those in the ODP group as non-radical (R1) resection. The reverse was performed in the worst-case analysis.

The primary endpoint is presented as the difference between the two groups with corresponding two-sided 90% confidence interval (CI) based on Wilson's score method. The lower limit of this 90% CI was compared with the predefined -7% non-inferiority margin to confirm the non-inferiority of MIDP, with the corresponding $p_{\text{non-inferiority}}$ following Dunnett and Gent.²⁴ We compared dichotomous data with Chi-square or Fisher's exact test (as appropriate), and present these as proportions and percentages. We compared continuous data with Mann-Whitney U test or independent samples t-test as appropriate, and present these as median with interquartile range (IQR) or mean with standard deviation (SD). Time-to-event outcomes (i.e., length of hospital stay, time to functional recovery, disease-free and overall survival, and time until start of chemotherapy) were analysed using Kaplan-Meier estimates and log-rank tests. To facilitate the comparison with previous trials, time to functional recovery and hospital stay were also analysed using conventional Mann-Whitney U tests. We also performed exploratory per-protocol analysis, which included only patients who received the allocated treatment for pancreatic cancer. We also performed sensitivity analysis (excluding neoadjuvant treatment) and post-hoc subgroup analysis (laparoscopic vs robotic procedures). Moreover, we performed a sensitivity analysis for functional recovery by excluding centres from the United States of America as these patients did not receive blinding, and by excluding patients with a complicated postoperative course (i.e., POPF, DGE, PPH, Clavien-Dindo grade ≥ 3). We performed a Cox proportional hazard analysis to identify predictors for overall survival. All covariates with a p-value <0.1 in the univariable models were included in one multivariable model. Hazard ratios for overall survival and disease-free survival of MIDP compared to ODP were calculated using univariable cox regression analysis. Quality of life outcomes were compared using a linear mixed model (see Appendix p 4). Health resource costs were calculated in Euros (€), compared using nonparametric bootstrapping (5000 samples), and presented as mean differences with

corresponding two-sided 95% bias corrected and accelerated confidence intervals (BCaCIs). See Appendix (pp 4–5) for a detailed description of quality of life and costs. All analyses were performed in SPSS for Macintosh, version 24.0 (IBM Corp., Orchard Road Armonk, New York, US), except for the time-to-event outcomes which were analysed using R (cran.r-project.org). A two-tailed p-value <0.05 was considered statistically significant. This trial is registered with the ISRCTN registry, number ISRCTN44897265.

Role of the funding source

Medtronic Covidien AG (Rheinfal, Switzerland) and Johnson & Johnson Medical Limited (Livingston, United Kingdom) funded the trial (investigator-initiated grant) to cover salary costs of the trial coordinators. The funders had no role in the design or conduct of the trial, the interpretation of the results, and the decision to publish. The first authors wrote the first draft of the manuscript; the senior authors revised and supervised this. All co-authors participated in study design, interpretation of data, and manuscript preparation.

Results

Between May 8, 2018 and May 7, 2021, 261 patients with resectable pancreatic cancer were randomly assigned to MIDP (132 patients) and ODP (129 patients) (Fig. 1). One patient in the MIDP group and two patients in the ODP group withdrew their consent for further study participation before surgery and were replaced according to protocol. Eventually, 131 patients in the MIDP group and 127 patients in the ODP group were included in the intention-to-treat population. The modified intention-to-treat population included 114 patients in the MIDP group and 110 patients in the ODP group after exclusion of 13 patients with unresectable disease at surgical exploration in each group, and one patient in the MIDP group who became inoperable before surgery due to impaired cardiac and pulmonary function, and 7 patients with missing data on primary endpoint (3 MIDP, 4 ODP). The per-protocol analyses included 94 patients in the MIDP group and 100 patients in the ODP group after the further exclusion of 37 patients: 20 patients because of non-PDAC diagnoses (8 in the MIDP group and 12 in the ODP group); 14 patients in the MIDP group because of conversion; one patient in the ODP group who received pancreatoduodenectomy because of tumor location; one patient in the ODP group who received enucleation because of intraoperative confirmation of a neuroendocrine tumor; and one patient in the MIDP group who was inoperable at time of surgery due to cardiac arrest and received ODP three months after initial surgery because of tumor progression. Baseline characteristics were well balanced for both the intention-to-treat, modified intention-to-

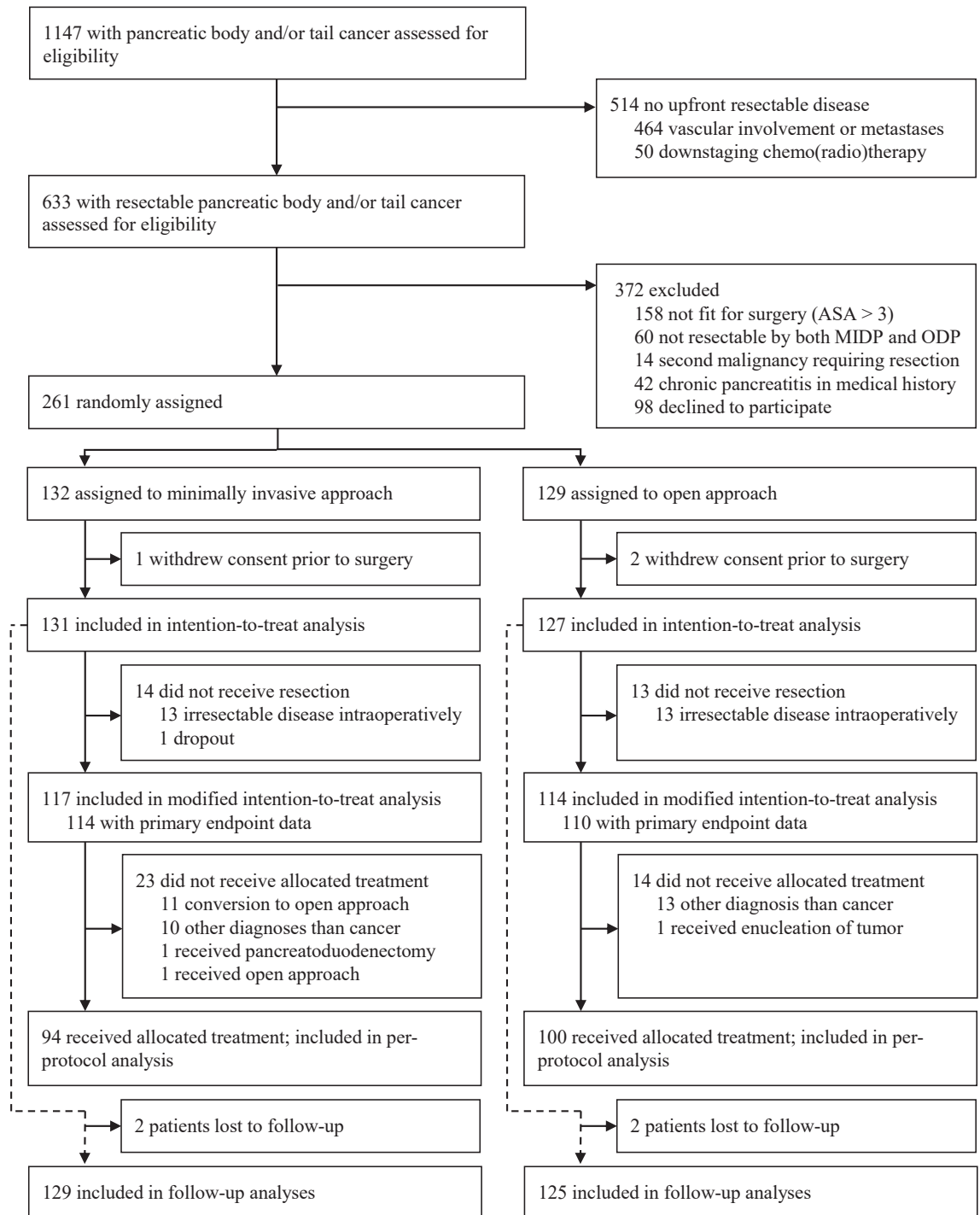


Fig. 1: Trial profile.

treat, and per-protocol populations (Table 1 and Appendix p 8, respectively).

The primary endpoint of R0 resection was achieved in 83 (73%) of 114 patients who underwent

MIDP and in 76 (69%) of 110 patients who underwent ODP (Table 2) when analysed by modified intention-to-treat. The absolute difference in primary endpoint was 3.7% (90% CI -6.2% to 13.6%), thus confirming

	MIDP group (n = 131)	ODP group (n = 127)
Age—yr.	69.2 (±8.4)	68.5 (±9.0)
Sex		
Male	63 (48.1)	68 (53.5)
Female	68 (51.9)	59 (46.5)
BMI—kg/m ²	25.2 (22.6–27.9)	25.8 (23.0–28.7)
ASA classification		
I	13 (9.9)	6 (4.7)
II	74 (56.5)	63 (49.6)
III	44 (33.6)	58 (45.7)
Prior abdominal surgery	89 (67.9)	77 (60.6)
Tumor location		
Pancreatic body	56 (42.7)	54 (42.5)
Pancreatic tail	56 (42.7)	49 (38.6)
Body–tail junction	19 (14.6)	24 (18.9)
Tumor size—mm	27.0 (20.0–36.0)	26.5 (20.0–40.0)
Splenic vessel involvement on imaging		
Vein involvement	24 (18.3)	20 (15.7)
Artery involvement	12 (9.2)	6 (4.7)
Both involved	36 (27.5)	38 (30.0)
Multivisceral involvement on imaging	9 (6.9)	12 (9.4)
Neoadjuvant treatment	23 (17.6)	28 (22.0)
Chemotherapy	19 (14.5)	22 (17.3)
Radiotherapy	0 (0.0)	1 (0.8)
Chemoradiation	4 (3.1)	5 (3.9)
Tumor markers at baseline		
CEA—ng/mL	2.8 (2.0–6.7)	2.9 (1.9–6.5)
CA 19–9—u/mL	50.0 (14.0–170.0)	47.3 (10.8–287.8)
Resection performed	117 (89.3)	114 (89.8)
Received distal pancreatectomy	116 (88.5)	112 (88.2)
Received pancreatoduodenectomy	1 (0.8)	1 (0.8)
Received enucleation	0 (0.0)	1 (0.8)
Received assigned procedure for pancreatic cancer	94 (71.8)	100 (78.7)

Categorical data are reported in numbers and frequencies. Normally distributed continuous data are reported in mean (SD). Non-normally distributed continuous data are reported in median (IQR). MIDP, Minimally invasive distal pancreatectomy; ODP, Open distal pancreatectomy; SD, Standard deviation; IQR, Interquartile range; BMI Body mass index; ASA, American Society of Anesthesiologists; CEA, Carcinoembryonic antigen; CA, Carbohydrate antigen; mL, Millilitre.

Table 1: Baseline characteristics of 258 patients undergoing distal pancreatectomy in the intention-to-treat population.

the non-inferiority of MIDP compared to ODP ($p_{\text{non-inferiority}} = 0.039$). Median lymph node yield was comparable between the two groups (22.0 [16.0–30.0] vs 23.0 [14.0–32.0], $p = 0.86$). The other histopathological outcomes also did not differ between the groups (Table 2).

Conversion was performed in 14 (12%) patients in the MIDP group. Most of them ($n = 10$) were non-urgent conversions because of unexpected tumor involvement of vascular structures ($n = 7$), adhesions ($n = 2$), or intraoperative conversion to pancreatoduodenectomy ($n = 1$). Urgent conversions occurred in four patients, which were all due to intraoperative bleeding. Robotic procedures were performed in 31 (27%) of 117 MIDP procedures. The median operative time was 31 min longer in the MIDP group (240 [IQR 175–309] vs 209 [IQR 158–257] minutes,

$p = 0.01$), whereas blood loss was less (although not statistically significant) after MIDP (200 [IQR 100–300] vs 200 [IQR 100–400], $p = 0.06$, Table 3).

Median time to functional recovery (5.0 [95% CI 4.5–5.5] days after MIDP vs 5.0 [95% CI 4.7–5.3] days after ODP, $p = 0.22$ when analysed by Kaplan–Meier estimates and log-rank test [for reference: $p = 0.03$ with Mann–Whitney U]) and total length of hospital stay (7.0 [95% CI 6.4–7.6] days after MIDP vs 7.0 [95% CI 6.3–7.7] days after ODP, $p = 0.96$ when analysed by Kaplan–Meier estimates and log-rank test [for reference: $p = 0.43$ with Mann–Whitney U]) were comparable. Other postoperative outcomes also did not differ between the two groups (Table 4). The rate of unplanned intensive care admission was less (although not statistically significant) after MIDP (5% vs 10%, $p = 0.08$), but the length of unplanned ICU stay was shorter in the

	MIDP group (n = 114) ^a	ODP group (n = 110) ^a	Risk difference (%) (90% CI)	p-value
Radicality of resection ^b				
Radical, R0 resection—≥1 mm	83 (72.8)	76 (69.1)	3.7 (–6.2 to 13.6)	0.039 (P _{non-inferiority})
Non-radical resection—<1 mm	31 (27.2)	34 (30.9)		
Lymph node yield	22.0 (16.0–30.0)	23.0 (14.0–32.0)		0.86
Positive lymph nodes	1.0 (0.0–3.0)	1.0 (0.0–3.0)		0.82
Histopathological tumor size—mm	30.0 (23.0–42.0)	29.0 (20.0–40.0)		0.56
Poor tumor differentiation	32 (31.7)	38 (40.9)		0.18
Perineural invasion	90 (78.9)	83 (75.5)		0.53
Lymphovascular invasion	77 (67.5)	72 (65.5)		0.74
T-stadium				0.89
T1	22 (19.3)	26 (23.6)		
T2	64 (56.1)	59 (53.7)		
T3	28 (24.6)	25 (22.7)		
T4	0 (0.0)	0 (0.0)		
N-stadium				0.08
N0	43 (37.7)	47 (42.7)		
N1	53 (46.5)	36 (32.7)		
N2	18 (15.8)	27 (24.5)		
M-stadium				NA
M0	114 (100.0)	110 (100.0)		
M1	0 (0.0)	0 (0.0)		
Histopathological diagnosis				0.98
Pancreatic cancer	107 (93.9)	101 (91.8)		
NET	3 (2.6)	3 (2.7)		
Other	4 (3.5)	6 (5.5)		

Categorical data are reported in numbers and frequencies. Continuous data are reported in median (IQR). MIDP, Minimally invasive distal pancreatectomy; ODP, Open distal pancreatectomy; IQR, Interquartile range; NET, Neuroendocrine tumor. ^aAnalyses were performed according to modified intention-to-treat since histopathology data were not available for patients with unresectable disease (n = 27) and for 7 patients with missing data on primary endpoint (3 MIDP, 4 ODP) because of different diagnosis. ^bAs measured at the transection and posterior margins.

Table 2: Histopathology outcomes in the (modified) intention-to-treat population.

MIDP group (median 1.0 [95% CI 0.4–1.6] day vs 4.0 [95% CI 2.6–5.4] days, p = 0.02). The rate of readmission was comparable between groups (22.1% vs 21.3%, p = 0.86; see [Appendix p 24–25](#)). Serious adverse events were reported in 23 (18%) of 131 patients in the MIDP group vs 28 (22%) of 127 patients in the ODP group. Protocol deviations are summarised in the [Appendix \(p 23\)](#).

During a median follow-up time of 23.5 (IQR 17.0–30.0) months, 100 (39%) of 258 patients died: 51 (40%) of 131 patients in the MIDP group and 49 (39%) of 127 patients in the ODP group ([Table 4](#)). Four patients were lost-to-follow-up (two in each group). In evaluable patients, one-year (77% vs 72%) and two-year survival rates (46% vs 48%) were comparable. The hazard ratio for overall survival was 0.99 (95% CI 0.67–1.46, p = 0.94; [Fig. 2a](#)). Recurrence or disease progression occurred in 58 (44%) of 131 patients in the MIDP group and in 55 (43%) of 127 patients in the ODP group after a median follow-up of 9 months in both groups. The hazard ratio for disease-free survival was 0.97 (95% CI 0.67–1.42, p = 0.88; [Fig. 2b](#)). In patients with recurrence or disease progression, the rate of local recurrence or disease progression was 26% after MIDP

and 25% after ODP. Adjuvant treatment was administered in 86 (66%) of 131 patients following MIDP and in 82 (65%) of 127 patients following ODP. Median time until start of adjuvant treatment was 57 (95% CI 51.5–62.5) days after MIDP and 57 (95% CI 50.6–63.4) days after ODP (p = 0.37). Age, radical resection, perineural invasion, and adjuvant chemotherapy were independent predictors for overall survival ([Appendix p 7](#)).

The per-protocol analysis failed to confirm non-inferiority (p_{non-inferiority} = 0.06; [Appendix p 9](#)), as did the worst-case scenario (p_{non-inferiority} = 0.098; [Appendix p 22](#)). The best-case scenario confirmed the non-inferiority (p_{non-inferiority} = 0.011; [Appendix p 22](#)). Sensitivity and subgroup analyses did not affect results ([Appendix pp 12–19](#)). Functional recovery was shorter after MIDP compared to ODP when excluding patients with Clavien-Dindo grade ≥3 complications (5.0 [95% CI 4.6–5.4] days after MIDP vs 5.0 [95% CI 4.7–5.3] days after ODP, p = 0.04) and grade B/C POPF (4.0 [95% CI 3.5–4.5] days after MIDP vs 5.0 [95% CI 4.7–5.3] days after ODP, p = 0.045), see [Appendix p 20](#). There were no significant differences in the global health status up to 6 months postoperatively ([Appendix p 6](#)). The median scar satisfaction score was improved in the MIDP group as

	MIDP group (n = 131)	ODP group (n = 127)	p-value
Operative time—min	240.0 (175.3–308.8)	209.0 (158.0–257.0)	0.01
Blood loss—mL	200.0 (100.0–300.0)	200.0 (100.0–400.0)	0.06
Multivisceral resection	17 (14.5)	21 (18.4)	0.43
Vascular resection	6 (5.1)	3 (2.6)	0.33
Conversion to ODP	14 (12.0)	–	–
Type of MIDP procedure ^a			
Laparoscopic	86 (73.5)	–	–
Robotic	31 (26.5)	–	–
Complications Clavien-Dindo grade ≥ III	25 (19.1)	26 (20.5)	0.78
Postoperative pancreatic fistula ^a			0.41
Grade B	25 (21.4)	19 (16.7)	
Grade C	0 (0.0)	1 (0.9)	
Delayed gastric emptying ^a			0.83
Grade B	1 (0.9)	1 (0.9)	
Grade C	1 (0.9)	2 (1.8)	
Postoperative pancreatic hemorrhage ^a			0.43
Grade B	2 (1.7)	4 (3.5)	
Grade C	1 (0.9)	0 (0.0)	
Reinterventions	22 (16.8)	21 (16.5)	0.96
Surgical reintervention	4 (3.1)	4 (3.1)	0.94
Radiological reintervention	16 (12.2)	12 (9.4)	0.21
Endoscopic reintervention	7 (5.3)	8 (6.3)	0.67
Postoperative transfusions	9 (6.9)	13 (10.2)	0.33
Surgical site infection	7 (5.3)	6 (4.7)	0.82
Unplanned ICU admission	6 (4.6)	13 (10.2)	0.08
Length of ICU admission—days ^b	1.0 (0.4–1.6)	4.0 (2.6–5.4)	0.02
Total length of stay—days ^b	7.0 (6.4–7.6)	7.0 (6.3–7.7)	0.96
Time to functional recovery—days ^b	5.0 (4.5–5.5)	5.0 (4.7–5.3)	0.22
Readmission	29 (22.1)	27 (21.3)	0.86
90-day mortality	2 (1.5)	3 (2.4)	0.63
Complication related	0 (0)	1 (0.8)	
Oncology related	2 (1.5)	2 (1.6)	
Mean total inpatient hospital costs ^c , euros, €	18,067 (15,910–20,524)	21,192 (15,804–30,633)	0.44

Categorical data are reported in numbers and frequencies. Continuous data are reported in median (IQR). MIDP, Minimally invasive distal pancreatectomy; ODP, Open distal pancreatectomy; IQR, Interquartile range; ICU, Intensive care unit; US, United States. ^aData on surgical parameters and pancreatic surgery specific complications were available for resected patients only (117 MIDP, 114 ODP). ^bLength of hospital stay and time to functional recovery are reported as medians with corresponding 95% confidence intervals, as calculated by Kaplan-Meier estimates and log-rank tests. For reference, when tested by Mann-Whitney U analyses, hospital stay was comparable (p = 0.43) and time to functional recovery was significantly shorter after MIDP (p = 0.03). ^cCosts are expressed for the year 2022, with corresponding 95% bias corrected and accelerated confidence intervals (BCaCIs).

Table 3: Intraoperative outcomes and postoperative outcomes up to 90 days in the intention-to-treat population.

compared to the ODP group (9.0 vs 8.0, p = 0.01, [Appendix p 21](#)). The mean costs of distal pancreatectomy and healthcare resources used up to 90 days postoperatively were comparable between the two groups (€18067 vs €21192; mean difference, €–3124; 95% BCaCI, –11056 to 4806).

Regarding the quality of patient blinding, 45 (38%) of 117 patients in the MIDP group and 67 (58%) of 114 patients in the ODP group reported to have undergone (i.e., guessed to have undergone) the opposite procedure. Patients who reported the other approach did not have a different time to functional recovery compared to patients who reported the correct approach. Pathologists reported the opposite procedure in 20 (17%) of 117

patients in the MIDP group and in 23 (22%) of 114 patients in the ODP group ([Appendix p 21](#)).

Discussion

This international multicentre randomised trial provides some evidence of the non-inferiority of MIDP (formally ‘left radical pancreatectomy’) for radical resection rate as compared to ODP in patients with resectable pancreatic cancer. Lymph node yield was comparable in both groups. MIDP was associated with longer operative time compared to ODP but better scar satisfaction scores at one year postoperatively. Other postoperative outcomes did not differ between groups.

	MIDP group (n = 131) ^a	ODP group (n = 127) ^a	p-value
Lost to follow-up	2 (1.5)	2 (1.6)	0.96
Survival rates ^b			
One-year survival	96 (76.8)	88 (72.1)	0.40
Two-year survival	41 (45.6)	42 (48.3)	0.72
Deceased during follow-up	51 (39.5)	49 (39.2)	0.96
Death cause during follow-up			0.12
Due to tumor-related causes	37 (72.5)	43 (87.8)	
Other causes	9 (17.6)	5 (10.2)	
Unknown cause	5 (9.8)	1 (2.0)	
Recurrence or progression ^c	58 (44.3)	55 (43.3)	0.98
Local	7 (12.1)	7 (12.7)	
Distant	43 (74.1)	41 (74.5)	
Local and distant	8 (13.8)	7 (12.7)	
Intraperitoneal recurrence	53 (40.5)	48 (37.8)	0.45
Recurrence free survival—months	9.0 (7.6–10.4)	8.0 (5.5–10.5)	0.10
Adjuvant therapy			0.85
Adjuvant chemotherapy	78 (59.5)	73 (57.5)	
Adjuvant radiotherapy	1 (0.8)	0 (0.0)	
Adjuvant chemoradiotherapy	7 (5.3)	9 (7.1)	
Time to adjuvant therapy—days	57 (51.5–62.5)	57 (50.6–63.4)	0.37
Tumor markers at one-year follow-up			
CEA—ng/mL	3.0 (2.0–5.3)	2.7 (1.5–5.4)	0.46
CA 19-9—u/mL	26.5 (9.0–84.0)	20.0 (5.3–137.0)	0.44

Categorical data are reported in numbers and frequencies. Normally distributed continuous data are reported in mean (SD). Non-normally distributed continuous data are reported in median (IQR). Time-to-event data are reported in median and 95% confidence interval. MIDP, Minimally invasive distal pancreatectomy; ODP, Open distal pancreatectomy; CEA, Carcinoembryonic antigen; CA, Carbohydrate antigen; mL, Millilitre. ^aData were available for 254 patients (129 MIDP and 125 ODP), four patients were lost to follow-up. ^bIn the intention-to-treat population, one-year survival was available for 247 patients (125 MIDP, 122 ODP), two-year survival was available in 177 patients (90 MIDP, 87 ODP). ^cIntraperitoneal progression or recurrence occurred in 33.6% in the MIDP group and in 33.1% in the ODP group (p = 0.93).

Table 4: Oncological outcomes in the intention-to-treat population.

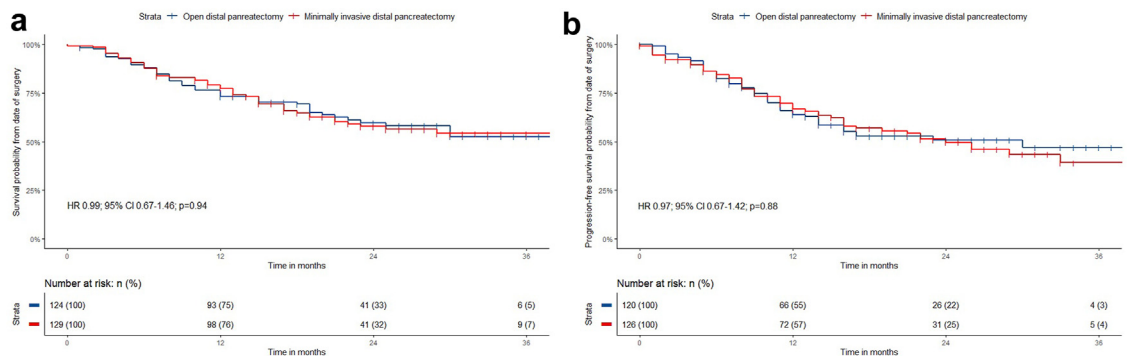


Fig. 2: Overall and disease-free survival after MIDP and ODP in patients with resectable pancreatic cancer according to intention-to-treat. Survival analyses were performed with Kaplan-Meier estimated and log-rank tests. a) Kaplan-Meier curves for overall survival, hazard ratio was 0.99 (95% CI 0.67–1.46, p = 0.94). b) Kaplan-Meier curves for disease-free survival, hazard ratio was 0.97 (95% CI 0.67–1.42, p = 0.88).

Previous retrospective studies raised concerns regarding the oncological safety of MIDP compared to ODP, but were subject to well-known flaws of retrospective studies, such as treatment allocation bias, the presence of learning curves for MIDP, and differences in definitions and protocols between studies and specimen handling between MIDP and ODP.¹⁰ The present study demonstrated some evidence of non-inferior

oncological outcomes in terms of radical resection rate after MIDP compared to ODP according to modified intention-to-treat and sensitivity analysis. The result of the per-protocol analysis ($p_{\text{non-inferiority}} = 0.06$) suggested to suspend judgment, but was hampered by a lack of power, because the point estimate of radicality of resection was in favour of MIDP over ODP. Although the worst-case scenario could not confirm non-

inferiority and the best-case scenario could, these situations are considered not very probable. Hence, this study supports the use of MIDP as a safe and feasible approach in this patient category. As this study was not designed to confirm superiority of the minimally invasive approach, it remains at the surgeon's discretion whether MIDP or ODP is best suitable for an individual patient. This should consider the surgeon's surgical experience and training as MIDP for pancreatic cancer is a more challenging procedure than MIDP for other indications. This is highlighted by the relatively high 12% conversion rate in this study (compared to the 3–8% conversion rate in two previous randomised trials with only 18–21% of pancreatic cancer). This increase was mainly related to progression to vascular involvement prior to MIDP, as this was the case in 50% of conversions. However, general outcomes of MIDP were good with low rates of post-pancreatectomy fistula, haemorrhage and delayed gastric emptying.

In a recent randomised trial in patients with cervical cancer, demonstrating worse survival rates after minimally invasive hysterectomy compared to open hysterectomy, the authors questioned whether the insufflation gas (CO₂) or different tumor manipulation in minimally invasive procedures might facilitate tumor spillage into the peritoneal cavity.¹¹ The similar rate of intraperitoneal recurrences found after MIDP and ODP in the present study (41% vs 38%, $p = 0.45$) seems to refute this theory for pancreatic cancer. Accordingly, reports of randomised trials on minimally invasive esophagectomy for oesophageal cancer and minimally invasive resection for colon cancer showed comparable oncological outcomes to open surgical resection.^{25,26} Tumor biology rather than surgical approach is probably the main factor driving dissemination of cancer and prognosis.

The technical feasibility of MIDP for pancreatic cancer was also questioned in previous studies.^{10,27} Main concerns were raised since the reported lymph node yield of MIDP was lower compared to ODP in several studies,¹⁰ which were fuelled by a recent study that reported a minimum requirement of 19–20 nodes for adequate postoperative staging.^{28,29} The present study showed comparable lymph node yield in both groups, with a higher yield (22–23 nodes in both MIDP and ODP) compared to previous studies. The use of standardised surgery and histopathological protocols might have contributed to this finding. Moreover, the technical applicability of MIDP for radical procedures (e.g., radical antegrade modular pancreatosplenectomy) was questioned and other procedures were proposed in previous studies.^{18,27} In the present study, procedures in the MIDP group were performed using the standardised 'no-touch' left radical pancreatosplenectomy,¹⁸ which follows the same oncological principles as the radical antegrade modular pancreatosplenectomy procedure,²⁰ permitting a local radicality and reducing the risk of intra-abdominal seeding. The outcomes of this study

show that surgeons are able to obtain the minimum oncological criteria required during distal pancreatectomy for pancreatic cancer through MIDP.¹⁹

In this study, no benefit for time to functional recovery, estimated blood loss, and length of hospital stay were seen in the MIDP group as has been reported in two previous randomised trials for MIDP vs ODP, when performed for all indications.^{7,8} The authors feel that this, among others, could be related to the large groups of 35 participating centres from 12 countries with multiple surgeons, which could have diluted treatment effects. Furthermore, distal pancreatectomy for cancer is known to be more challenging than distal pancreatectomy for benign or premalignant disease. The two previous randomised trials^{7,8} only included a minority (45%) of patients with pancreatic cancer. Therefore, it could be that the advantages of minimally invasive surgery are less prominent in this subgroup of patients. Analyses for blood loss did show a trend towards less blood loss in MIDP (200 [IQR 100–300] vs 200 [IQR 100–400]), but this did not reach statistical significance, possibly due to type II error. When excluding patients with complicated postoperative course (i.e., Clavien-Dindo ≥ 3 and POPF), time to functional recovery was significantly shorter after MIDP ($p = 0.04$). Hence, in patients with an uncomplicated postoperative course, MIDP might provide benefits in terms of shorter time to functional recovery. Possible other benefits in the present study were shorter unplanned ICU admission, and improved scar satisfaction scores compared to ODP at one year postoperatively (also previously reported in the long-term report of the LEOPARD trial³⁰). Furthermore, when analysing time to functional recovery after MIDP and ODP with a Mann-Whitney U test (as done previously in the LEOPARD and LAPOP trials^{7,8}), rather than with a 'time to event approach' as done in the present study, we found a significant shorter time to functional recovery after MIDP compared to ODP ($p = 0.03$).

This study has several limitations that should be considered. First, the ideal primary endpoint for this trial would have been survival, but this would require >1000 patients to be enrolled and was therefore considered not feasible for this indication. Radicality of resection reflects oncological safety of surgical procedures and was associated with survival in several studies,³¹ which was therefore chosen as primary endpoint of this study. Second, primary endpoint assessment did not include the anterior surface, which has demonstrated prognostic significance in a recent study.³² However, the aim of the present study was to evaluate the feasibility of MIDP at 'surgical margins', which only included the posterior and transection margins. Third, the preoperative imaging interval of maximum 4 weeks was exceeded in 40 (16%) of 258 patients. This was, however, considered of small impact as four (10%) of these patients had unresectable disease (i.e., occult metastatic disease) at surgical exploration,

whereas 23 (11%) of 218 patients with an interval <4 weeks had unresectable disease (i.e., occult metastatic disease) at surgical exploration. Fourth, 9% of patients had other diagnoses than pancreatic cancer in which primary outcome assessment of radical resection was not possible. Although undesirable, this reflects the diagnostic difficulties during the work-up of patients affected by suspected resectable pancreatic cancer. Moreover, this rate is comparable to previously reported in studies.^{33,34} Central pathology review was not performed but would not have changed this finding as preoperative pathological confirmation was not mandatory given the pragmatic design of the present study. Fifth, data on functional recovery were not available for 27 patients since these data were not collected in patients who did not undergo a resection. Although this somewhat limited the statistical power, it was considered of low impact. Sixth, neoadjuvant treatment was initially set as exclusion criteria for this study because of surgical difficulties and lack of consensus on resection margin reporting among different pathologists.³⁵ Randomised evidence is lacking on the benefit of neoadjuvant treatment in patients with left-sided primary resectable pancreatic cancer. Several randomised trials are either recently completed (NCT02919787) or are currently underway on neoadjuvant therapy in resectable pancreatic cancer (e.g., NCT04340141 and NCT04927780). However, given the growing experience in minimally invasive surgery after neoadjuvant treatment, it was agreed that these patients could be included based on the surgeon's discretion as long as these patients had upfront resectable disease. Patients with neoadjuvant treatment were well balanced between the two groups (18% vs 22%) and sensitivity analyses showed no impact of the inclusion of neoadjuvant treatment on outcomes. Seventh, median survival was not reached. However, no significant differences in postoperative survival are expected considering the overlapping survival curves in this study. Eighth, due to the Covid pandemic operating theatre availability was reduced over the majority of the inclusion period. Nevertheless, on average 6 patients were included per centre per year out of on average 11 patients with upfront resectable pancreatic cancer per centre per year. Ninth, although the rates of grade B/C POPF did not differ between groups, differences between pancreatic transection methods in centres could have influenced outcomes. The study protocol included standardised transection at the pancreatic neck with a preference for stapling of the pancreas. Furthermore, two previous randomised trials did not find differences in rates of POPF between stapler transection, handsewn closure, and ultrasonic dissector.^{36,37} Stratification per centre could have minimised the impact of differences between centres, but was not performed as the resulting high number of strata would have hampered the randomisation process. The strengths of this trial lay in the well-standardised surgical and pathological procedures

with blinded endpoint assessment (i.e., blinding of patients and pathologists) to minimize the impact of these confounding factors. This was considered successful, as 45% of patients and 77% of pathologist were not able to correctly guess the type of surgical approach (Appendix p 21). Moreover, outcomes in this study were comparable among participating centres, allowing the results to be universal and reproducible.

In conclusion, this randomised controlled trial provides some evidence of non-inferior radical resection rates after MIDP as compared to ODP in patients with resectable pancreatic body and tail cancer. This supports the use of minimally invasive surgery in this patient category. It remains at the surgeons' discretion to decide whether a minimally invasive or open approach is suitable for an individual patient.

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Data sharing statement

Deidentified individual participant data collected in the DIPLOMA trial can be made available upon request. Please contact the principal investigators (MAH and MGB) who will review all requests. The DIPLOMA investigators will be allowed to approve all research performed with the shared data.

Declaration of interests

Tobias Keck is a member of the advisory board for Olympus, Medtronic, and Dexter. Daan Lips received a proctoring grant by Intuitive Surgical. Marc Besselink and Mohammad Abu Hilal received Investigator Initiated Research grants by Medtronic (DIPLOMA trial), Ethicon (DIPLOMA trial and E-MIPS registry), and Intuitive Surgical (E-MIPS registry) and proctoring grants for Dutch and European training programs in robotic pancreatoduodenectomy by Intuitive Surgical. The other authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanepe.2023.100673>.

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