NEJM Evidence

Published November 25, 2025
NEJM Evid 2025;4(12)
DOI: 10.1056/EVIDoa2500045

ORIGINAL ARTICLE

Minimally Invasive versus Open Pancreatoduodenectomy for Resectable Neoplasms

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Abstract

BACKGROUND Minimally invasive pancreatoduodenectomy (MIPD) might accelerate postoperative recovery in patients with primary resectable neoplasm compared with open pancreatoduodenectomy (OPD), although the safety of MIPD remains debated. We aimed to assess whether MIPD is noninferior to OPD for overall complications and superior for time to functional recovery (TTFR).

METHODS We conducted an international, multicenter, patient-blinded randomized noninferiority trial in patients undergoing pancreatoduodenectomy for primary resectable pancreatic and periampullary neoplasm from high-volume centers. Patients were randomly assigned in a 2:1 ratio to undergo robot-assisted or laparoscopic MIPD versus OPD and were blinded to the procedure until postoperative day 5. The primary end point was overall complications within 90 days of surgery, as measured using the Comprehensive Complication Index (range 0–100, with higher scores indicating more severe complications). Noninferiority was tested using a margin of −7.5 points (one-sided 97.5% confidence interval [CI]; P<0.025 for noninferiority). The main secondary end point was TTFR, tested for superiority. Analyses were reported by the intention-to-treat principle.

RESULTS Overall, 288 patients were randomly assigned (190 MIPD [170 robot-assisted, 20 laparoscopic] and 98 OPD) in 14 centers. The mean Comprehensive Complication Index was 33.4±27.5 in the MIPD group versus 35.3±25.5 in the OPD group (mean difference, −1.9; 95% CI, −8.5 to 4.7; P=0.002 for nonferiority). In the MIPD group, the median TTFR was 7 days (95% CI, 6 to 8) versus 8 days (95% CI, 7 to 11) in the OPD group. The MIPD conversion rate to open surgery was 8.4%. Rates of postoperative pancreatic fistula were 22.6% versus 35.7% (relative risk 0.63; 95% CI, 0.43 to 0.91) and were 12.6% versus 22.7% (relative risk 0.57; 95% CI, 0.32 to 0.98) for surgical site infection after MIPD and OPD, respectively. Death by 90 days occurred in 4.7% of patients after MIPD versus 2.0% after OPD (relative risk 2.40; 95% CI, 0.51 to 11.30).

CONCLUSIONS In patients with resectable pancreatic and periampullary neoplasm, MIPD was noninferior to OPD for 90-day overall complications (Funded by Intuitive Surgical

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and Fondazione Poliambulanza Istituto Ospedaliero; International Standard Randomised Controlled Trial Number Registry, ISRCTN27483786.)

Background

Pancreatoduodenectomy is a complex surgical procedure used to treat neoplasms in the pancreatic head and periampullary region. Following pancreatoduodenectomy, approximately 30%–40% of patients require postoperative interventions for surgical complications, affecting time to functional recovery (TTFR), quality of life, and health care resources.[1] Therefore, innovative surgical techniques and treatment strategies are sought to improve outcomes for this highly complex and low-volume procedure.

Minimally invasive pancreatoduodenectomy (MIPD) aims to improve patient outcomes by reducing the impact of surgery.[2-4] However, there has been considerable reluctance to embrace MIPD as an alternative to open pancreatoduodenectomy (OPD), which has been especially fueled by the premature termination of the multicenter LEOPARD-2 (Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours) trial due to safety concerns with laparoscopic MIPD.[5] Although other randomized trials reported small benefits of laparoscopic MIPD, safety concerns remain.[6-9] Investigations of robotic MIPD have also yielded mixed results. Recently, a single-center phase 2 randomized trial from Germany reported a higher rate of pancreatic surgery–specific complications following robotic MIPD, no reduction in hospital stay, and a 23% conversion rate to OPD.[10] On the other hand, a recent multicenter phase 3 randomized trial from China reported shorter hospital stays among patients after robotic MIPD without benefits in terms of complication rates compared with OPD.[11]

An international, multicenter randomized trial comparing MIPD with OPD in experienced high-volume centers, where surgeons have surpassed the initial learning curve, is currently lacking. Such a trial is needed to assess the safety and potential benefits of MIPD, which need to be weighed against the potentially higher costs of MIPD. Therefore, the DIPLOMA-2 trial primarily aimed to investigate the safety of robotic and laparoscopic MIPD (noninferiority design) in terms of morbidity and mortality rate and, secondarily, TTFR, surgery-specific complications, quality of life, and costs.

Methods

The investigator-initiated, international, multicenter, patient-blinded noninferiority randomized controlled DIPLOMA-2 trial compared MIPD (robotic and laparoscopic) with OPD in patients with a primary resectable neoplasm in the pancreatic head and periampullary region. The trial was conducted in 14 high-volume centers across 6 countries collaborating in the European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS).

Patient inclusion started after approval of the trial protocol by the primary medical ethical review committees in Amsterdam University Medical Center (Amsterdam UMC), in Amsterdam, the Netherlands, and Fondazione Poliambulanza Hospital Institute, in Brescia, Italy. Local ethics approval was obtained for every participating center. The trial is registered in the International Standard Randomised Controlled Trial Number Registry (ISRCTN27483786), and the trial protocol has been published.[12] Written informed consent was obtained from each patient. The trial was reported according to the Consolidated Standards of Reporting Trials guidelines for randomized controlled trials. Clinical trial monitoring was performed by an independent monitor from Amsterdam UMC. An independent data and safety monitoring committee assessed patient recruitment and repeated patient safety evaluations at three time points during the recruitment phase.

TRIAL POPULATION AND CENTERS

Adult patients with an indication for elective pancreatoduodenectomy because of pathology-proven or clinically suspected pancreatic and periampullary neoplasm without any (0°) vascular contact were assessed for eligibility (i.e., primary resectable neoplasm). Patients who received neoadjuvant chemotherapy were considered eligible only if the tumor was upfront resectable (i.e., without vascular contact).[13] Exclusion criteria were a body-mass index (BMI) of more than 35 (the body-mass index is the weight in kilograms divided by the square of the height in meters), distant metastases, (history of) chronic pancreatitis, and pregnancy.

The required minimum annual center volume, prior to trial participation, was a total of 30 MIPD and 30 OPD procedures per year. As a quality standard, the minimum personal lifetime experience of the primary surgeon within the trial was 60 MIPD procedures and 60 OPD procedures.

Centers participated in either robotic or laparoscopic MIPD, depending on their expertise. To participate in the trial, all surgeons performing MIPD were required to have successfully participated in an endorsed MIPD training program. Alternatively, surgeons were required to send a recorded and anonymized video of a personally performed MIPD procedure before the start of the trial, which was evaluated by the trial team, to be endorsed in trial participation. All MIPD procedures within the DIPLOMA-2 trial were video recorded and stored. An independent data and safety monitoring committee was established for the trial to continuously monitor patient safety throughout the inclusion period and to conduct interim reviews of the safety end points.

RANDOM ASSIGNMENT AND BLINDING

Patients were randomly allocated in a 2:1 ratio to MIPD and OPD. The 2:1 ratio was chosen to maintain a sufficient MIPD volume during the trial. Randomization was performed by the trial coordinators using an online computer-controlled permuted-block randomization module (Castor EDC, Ciwit, Amsterdam, the Netherlands) with concealed block sizes varying between 3, 6, and 9 patients.[14] Randomization was stratified for the minimally invasive technique group (robot-assisted or laparoscopic), the preoperative pancreatic fistula risk group (normal risk: pancreatic duct diameter ≥3 mm and BMI ≤25; versus high risk: pancreatic duct diameter <3 mm or BMI >25 on preoperative imaging), and the indication (pancreatic ductal adenocarcinoma vs. other).

For logistical reasons, it was not deemed possible to blind the assessors of the primary outcome. Therefore, an adjudication committee, blinded for treatment allocation, assessed the primary outcome of each included patient. Regarding the most important secondary outcome, TTFR, patients were blinded for treatment allocation preoperatively and until 5 days after surgery. Directly after skin closure, while the patient was still under general anesthesia, they received a firmly taped 40×40 cm abdominal dressing covering the incision(s) in an attempt to ensure their treatment allocation remained blinded (minimally invasive or open). This abdominal dressing was removed either on postoperative day 5 or earlier, when all criteria for functional recovery were met or there were medical reasons, such as a suspicion of wound infection. The success of blinding was assessed using the blinding index as proposed by Bang et al.[15] Patients were asked on day 2 and before dressing removal about treatment allocation, based on five categories: (1) strongly believe it was MIPD, (2) somewhat believe it was MIPD, (3) do not know, (4) somewhat believe it was OPD, and (5) strongly believe it was OPD. Patient blinding was also performed in patients who were converted to open surgery. Patient blinding was not performed in patients who underwent no resection due to occult metastases or locally advanced disease diagnosed during surgery

PROCEDURES, SURGICAL TECHNIQUE, AND POSTOPERATIVE REGIMEN

Patients were screened for eligibility in each individual participating center during local multidisciplinary meetings. In case of (suspected) malignancy, an abdominal computed tomography scan that was a maximum of 4 weeks (28 days) old at the time of surgery was required to minimize the risk of including patients with vascular contact or distant metastases. Because of the pragmatic design of the DIPLOMA-2 trial, MIPD and OPD procedures were performed according to the local/hospital/surgeon standards. All procedure details were recorded in an online case report form immediately after surgery. Patients were followed at the outpatient clinic according to local protocols. No directions or restrictions regarding postoperative care, blood tests, drain management, the use of medication, or other kinds of cointervention were given.

Participating centers were instructed to provide the same postoperative care for both trial groups based on enhanced recovery principles, which include early mobilization and expanding oral intake as desired by the patient.[16] Any incision used for reasons other than trocar placement and specimen extraction was defined as conversion. Patients allocated to the MIPD group who underwent conversion to OPD were analyzed in the MIPD group, according to the intention-to-treat principle. Reasons for conversion were categorized as urgent or nonurgent conversions.[17]

PRIMARY END POINT

The primary end point was overall complications up to 90 days post operation, as measured by the Comprehensive Complication Index (CCI). The CCI score was developed to reflect the cumulative postoperative morbidity based on the Clavien–Dindo classification of complications, and is validated for pancreatic surgery.[18-20] The CCI scores range from 0 (no complication of any kind during the postoperative period) to 100 (death of the patient). A detailed description of the CCI calculation within the DIPLOMA-2 trial can be found in the Supplementary Appendix (page 10).

SECONDARY END POINTS

The main predefined secondary end point (including a sample size calculation) was postoperative TTFR. Functional recovery, as defined by previous randomized trials,[21,22] was reached when all of the following criteria were met: (1) adequate pain control with oral analgesia only, (2) restoration of mobility to an independent level (or to preoperative level if previously impaired), (3) ability to maintain sufficient caloric intake (minimum 50% of required calories), (4) absence of intravenous fluid administration, and (5) no signs of active infection (no fever, decreasing C-reactive protein level below 150 mg/l). In addition, to assess postoperative daily activity up to 90 days, patients were asked to wear a Fitbit Inspire 2 device to record their daily step counts (as a measure of physical activity) and heart rate, combined as total active minutes per day.[23-26] A comprehensive overview of the outcomes of the postoperative activity tracking is not reported herein.

Other secondary end points included intraoperative parameters (type of surgery: robotic vs. laparoscopic), conversion (urgent or nonurgent), method of anastomosis, vascular resection, operative time, and blood loss. Surgeon-reported outcomes were collected using the National Aeronautics and Space Administration Task Load Index questionnaire following each procedure, which includes six task indicators: mental demand, physical demand, temporal demand, performance, frustration, and effort. Postoperative outcomes (up to 90 days after surgery) included major complications (defined as a Clavien–Dindo grade III or higher) and death (and whether this was related to surgical complications), postoperative pancreatic fistula grade B or C,[27] postpancreatectomy hemorrhage grade B or C,[28] bile leak grade B or C,[29] delayed gastric emptying grade B or C,[30] chyle leak grade B or C,[31] surgical site infection,[32] postoperative intervention (surgical, radiologic, or endoscopic), (length of) intensive care unit admission, (multi)organ failure, length of hospital stay, readmission, (time to) start of adjuvant therapy, and pathological outcomes (pathological diagnosis, tumor size, histology, and tumor grading),[33] distance from the tumor to all margins, and number of retrieved (positive) lymph nodes. Quality-of-life outcomes using the validated EuroQol 5 Dimensions five-level questionnaire (which uses scores ranging from −0.39 to 1, with higher scores indicating a better quality of life), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (which ranges from scores 0 to 100, with higher scores for the functional and general health status domains indicating better functional status and quality of life, and higher scores for the symptom domains and items indicating more severe symptoms), and the European Organization for Research and Treatment of Cancer pancreatic cancer module (QLQ-PAN26) (which ranges from scores 0 to 100, with higher scores indicating greater symptom burden) questionnaires with additional questions regarding scar complications and body image at baseline and at 1, 3, and 6 months after surgery were compared.[34,35] Further details, including questionnaire descriptions and minimal clinically important difference values, are provided in the Supplementary Appendix, pages 12–13.

All data were collected using standardized online case report forms by the local treating physicians. All outcome data were cross-checked with source data by the trial coordinators after the 90-day follow-up period was completed.

STATISTICAL ANALYSIS

The DIPLOMA-2 trial was designed as a noninferiority trial, hypothesizing that the mean 90-day CCI score for MIPD would be noninferior to OPD. In addition, the trial was powered to analyze the superiority of MIPD to OPD regarding TTFR in days. Full details about the sample-size calculation, including considerations for clinical relevance, are provided in the published trial protocol.[12] The sample size was calculated using PASS 2022 software to achieve 80% power ($1 - \beta$) in a per-protocol analysis with the following assumptions: 2.5% one-sided significance level (α), expected difference of the mean CCI score in the MIPD and OPD groups of 0 points, and a noninferiority margin of 7.5 points, with a standard deviation of 20 points in both groups, including 5% metastasized disease, a 10% conversion rate, and a 3% lost-to-follow-up rate after randomization leads to a total number of patients for random assignment of 288 (192 in the MIPD trial group and 96 in the OPD trial group). For TTFR (measured in days), which was analyzed with a Gehan–Breslow–Wilcoxon and log-rank test in their standard two-sided forms using the log-rank test, a sample of 247 patients (159 in the MIPD group and 88 in the OPD group) in a per-protocol analysis achieves 80% power to detect a 28% reduction in days (i.e., 6.5 days in the MIPD group; hazard ratio=0.72).

Primary and secondary end points were cross-checked with data from primary sources, and a blinded adjudication committee checked the definitions used. There were no patients with missing data for the primary end point and a few with missing data for secondary end points. No data were imputed. Primary and secondary end point data of all randomly assigned patients were analyzed based on three analysis sets. The modified intention-to-treat set

comprises all patients in the group to which they were randomly assigned (converted patients remain in the MIPD group) and served as the primary analysis set. Patients with preoperatively diagnosed tumor progression (vascular involvement or metastasized disease on repeated imaging), or patients who withdrew consent before surgery, were excluded and replaced. The per-protocol set consisted of all patients treated per protocol without major protocol violations and without conversions. In addition, the as-treated set was analyzed considering the patients in the group of the intervention that was performed (i.e., converted patients in the OPD group).

The primary outcome measure, CCI, was expressed as means (standard deviations) and tested for noninferiority using independent samples t-tests. Noninferiority was concluded if the upper limit of the one-sided 97.5% CI for the between-group difference was below the predefined noninferiority margin. The most important secondary outcome measure, TTFR, was tested two-sided for superiority using a Gehan–Breslow–Wilcoxon test. In addition, the individual TTFR criteria were analyzed descriptively and presented separately. The distribution of variables was determined using several plots (boxplot, Q–Q plot, and histogram) and Kolmogorov–Smirnov and Shapiro–Wilk tests. Other non–normally distributed continuous variables are expressed as medians (interquartile ranges [IQRs]) and were compared using the Mann–Whitney U test. Categorical variables, expressed as proportions, were compared by chi-square or Fisher's exact tests as appropriate. There was no adjustment for multiple testing in secondary end points, and the CIs were not adjusted for multiplicity; hence, a P value is assigned only for the primary outcome, CCI, and the predefined main secondary end point, TTFR, and CIs should not be used to infer clinical benefit. See Supplementary Appendix, pages 12–13, for a detailed description of quality of life.

The following prespecified subgroup and sensitivity analyses were performed: (1) comparison of MIPD and OPD in patients with major complications (Clavien–Dindo grade ≥III) and in patients without major complications (no complication or Clavien–Dindo grade I or II) separately; (2) comparison of centers for low and high annual MIPD volume during the trial separately (<20 MIPD/year vs. ≥20 MIPDs/year); (3) comparison of MIPD and OPD in patients with pancreatic ductal adenocarcinoma separately; (4) comparison of the rate of postoperative pancreatic fistula in MIPD and OPD for the International Study Group for Pancreatic Surgery subgroups of postoperative pancreatic fistula risk (A-B-C variant);[36,37] (5) comparison of robotic MIPD and OPD for the primary outcome, CCI, TTFR, and other outcomes (i.e., sensitivity analysis excluding laparoscopic MIPD); and (6) comparison of laparoscopic MIPD and OPD for the primary outcome, CCI, TTFR, and other outcomes (i.e., sensitivity analysis excluding robotic MIPD).

All analyses were performed in SPSS for Macintosh version 26.0 (IBM, New York, New York, USA), RStudio (cran.r-project.org), and SAS (version 9.3 or earlier; SAS Institute, Cary, North Carolina, USA).

Results

From January 2022 through July 2023, 302 patients were enrolled in 14 centers; 199 were randomly assigned to undergo MIPD and 102 to undergo OPD (Fig. 1). Overall, 13 patients (9 assigned to MIPD (4.5%) and 4 (3.9%) assigned to OPD) did not undergo surgery and were replaced in accordance with the trial protocol, 12 patients had vascular contact on repeat preoperative imaging, and 1 patient withdrew consent before surgery. The primary analysis of the trial (modified intention to treat) included 288 patients: 190 for MIPD (170 robotic and 20 laparoscopic) and 98 for OPD. The baseline characteristics of the enrolled patients are summarized in Table 1 and were well balanced between groups. In total, 84 (29.2%) patients underwent surgery for pancreatic ductal adenocarcinoma and 128 (44.4%) for other malignant diseases (Table 2). Details on the demographic characteristics and representativeness of the study population are provided in Table S20.

The median annual volume of MIPD (i.e., randomly assigned patients) per center was 22 (IQR 15–30), with 11 out of 14 centers (79%) performing more than 20 MIPD procedures per year during the trial.

SURGICAL FINDINGS

Among the included trial population, five patients (1.7%) did not undergo resection due to occult metastases or locally advanced disease diagnosed during surgery (Table 2). Robotic MIPD procedures were most common, accounting for 170 (89.5%) of the 190 MIPD procedures. A total of 16 out of 190 MIPD procedures (8.4%) were converted intraoperatively to OPD, including 2 of the 20 (10.0%) laparoscopic MIPD procedures and 14 of the 170 (8.2%) robotic MIPD procedures. Of these, 12 conversions (6.3%) were nonurgent conversions due to unexpected tumor involvement of vascular structures or adhesions. Four conversions (2.1%) were urgent due to bleeding. One patient randomly assigned to MIPD directly received open surgery due to

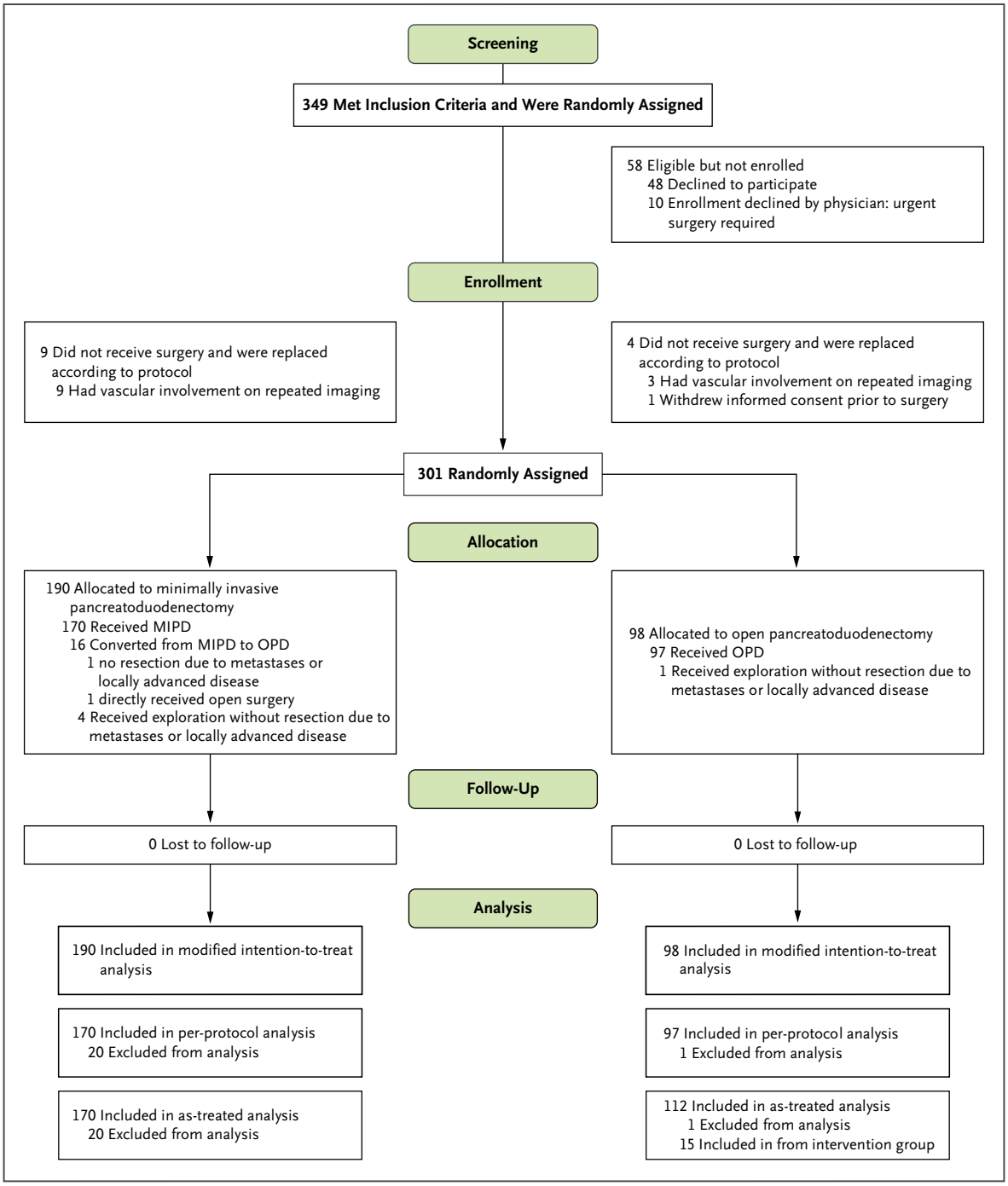

Figure 1. Trial Flowchart.

CONSORT denotes Consolidated Standards of Reporting Trials; MIPD, minimally invasive pancreatoduodenectomy; and OPD, open pancreatoduodenectomy.

pneumoperitoneum causing ventilation problems. The median operative time was 47 minutes longer in the MIPD group (MIPD 339 [IQR 280–3420] vs. OPD 292 [IQR 227–345] minutes), whereas estimated blood loss was 125 ml less after MIPD (175 ml [IQR 100–300] vs. 300 ml [IQR 130–500]) (Table 3). In the MIPD group, pylorus-resecting procedures were performed in 54% of patients (95% CI, 47–61) versus 30% (95% CI, 22–40) in the OPD group. Results of

Table 1. Characteristics of the Participants (Modified Intention-to-Treat Population).

Characteristic	Minimally Invasive PD (N=190)	Open PD (N=98)
Age (IQR) — years	70.0 (63.0–76.0)	68.0 (59.0–74.0)
Male sex — no. (%)	112 (58.9)	56 (57.1)
Body-mass index* — median (IQR)	24.8 (22.1–27.5)	24.8 (23.1–27.6)
Abdominal surgery in medical history — no. (%)	66 (36.1)	28 (30.4)
Diabetes mellitus in medical history — no. (%)	38 (20.0)	20 (20.4)
Preoperative biliary drainage — no. (%)	99 (53.5)	51 (52.6)
ASA physical status — no. (%)†		
1	8 (4.3)	5 (5.2)
2	114 (60.6)	60 (61.9)
3	65 (34.6)	32 (33.0)
4	1 (0.5)	0 (0.0)
WHO physical status — no. (%)‡		
0	126 (67.4)	74 (77.9)
1	57 (30.5)	18 (18.9)
2	4 (2.1)	3 (3.2)
Tumor size on imaging — median (IQR) mm	20 (12–30)	20 (12–29)
Preoperative pancreatic duct size ≥3 mm	120 (72.3)	63 (73.3)
High preoperative risk for postoperative pancreatic fistula — no. (%)§	121 (63.7)	60 (61.2)
Neoadjuvant therapy — no. (%)¶	12 (6.7)	6 (6.5)

* The body-mass index is the weight in kilograms divided by the square of the height in meters. ASA denotes American Society of Anesthesiologists; IQR, interquartile range; PD, pancreatoduodenectomy; and WHO, World Health Organization.
† American Society of Anesthesiologists physical status: 1 = normal healthy patient, 2 = mild systemic disease, 3 = severe systemic disease, and 4 = severe systemic disease that is a constant threat to life.
‡ World Health Organization physical status: 0 = fully active; 1 = restricted in strenuous activity but ambulatory; and 2 = ambulatory but unable to work, requiring some assistance.
§ High preoperative risk for postoperative pancreatic fistula was based on preoperative pancreatic duct size (<3 mm) and body-mass index ≥25.
¶ Neoadjuvant therapy includes chemotherapy or radiation therapy administered before surgery. Data were missing for: sex (N=1), body-mass index (N=1), abdominal surgery in medical history (N=13), preoperative biliary drainage (N=6), American Society of Anesthesiologists physical status (N=3), World Health Organization physical status (N=6), tumor size on imaging (N=91), preoperative pancreatic duct size ≥3 mm (N=36), and neoadjuvant therapy (N=5).

the National Aeronautics and Space Administration Task Load Index questionnaires are presented in Figure S5 and Table S15. Surgeons perceived higher mental demand (median 9 [IQR 5–11] vs. 7 [IQR 3–10]) and time pressure (median 4 [IQR 2–6] vs. 3 [IQR 1–7]) during MIPD compared with OPD (Table S15). The number (percentage) of patients successfully blinded after surgery, defined as blinded up to postoperative day 5, was 157 (84.9%) after MIPD and 82 (84.5%) after OPD (Table S6).

PRIMARY AND SECONDARY END POINTS

In the modified intention-to-treat analysis, the primary end point CCI score was 33.4±27.5 in the MIPD group versus 35.3±25.5 in the OPD group (difference in means [95% CI]: −1.9 [−8.5 to 4.7]), which met criteria for noninferiority (P=0.002 for noninferiority) (Table 3). The median TTFR, the predefined main secondary end point, was 7 days (IQR 6–14) after MIPD versus 8 days (IQR 5–11) after OPD (Gehan–Breslow–Wilcoxon test, P=0.024; Fig. 2 and Table S6). In a post hoc analysis using the log-rank test, the median TTFR was 7 days (IQR 6–14) after MIPD versus 8 days (IQR 5–11) after OPD.

The median length of hospital stay was 9 days (IQR 6–15) after MIPD versus 11 days (IQR 7–20) after OPD. At postoperative day 30, the median daily step count was 2711 (IQR 514–4803) in the MIPD group and 2034 (IQR 371–4087) in the OPD group. Other secondary outcomes of mortality and morbidity rates are shown in Table 3. The rate of postoperative pancreatic fistula grade B or C was 23% after MIPD versus 36% after OPD. Within 90 days of surgery, there were 11 deaths (3.8%) among the 288 patients: 9 (4.7%) in the MIPD group versus 2 (2.0%) in the OPD group. Further details about the deaths are described in Table S16.

Table 2. Surgical Characteristics and Histopathology (Modified Intention-to-Treat Population).*

Characteristic	Minimally Invasive PD (N=190)	Open PD (N=98)
No resection performed (intraoperatively diagnosed advanced disease/metastasis) — no. (%)	5 (2.6)	1 (1.0)
Robot-assisted procedure — no. (%)	170 (89.5)	—
Conversion to open surgery — no. (%)†	16 (8.4)	—
Laparoscopic to open surgery	2/20 (10.0)	—
Robot-assisted to open surgery	14/170 (8.2)	—
Soft/normal pancreatic texture — no. (%)‡	62 (33.2)	30 (30.6)
Pancreatic duct diameter — median (IQR) mm§	3 (2–4)	3 (2–5)
Type of procedure — no. (%)		
Pylorus-preserving PD	46 (24.2)	50 (51.0)
Pylorus resection PD/classic Whipple	137 (72.1)	47 (48.0)
Type of pancreatic anastomosis — no. (%)		
Pancreaticojejunostomy duct-to-mucosa	153 (80.5)	76 (77.6)
Pancreaticojejunostomy — dunking/invagination	27 (14.2)	18 (18.4)
Pancreatogastrostomy duct-to-mucosa	1 (0.5)	0 (0)
Pancreatogastrostomy — dunking/invagination	2 (1.1)	3 (3.1)
Intraoperative pancreatic stent placement	157 (85.3)	41 (42.3)
Intraoperative drain placement	177 (93.2)	93 (94.9)
Histopathology diagnosis — no. (%)		
Adenocarcinoma	146 (76.8)	66 (67.3)
Pancreatic ductal adenocarcinoma	58 (30.5)	26 (26.5)
Distal cholangiocarcinoma	31 (16.3)	14 (14.3)
Ampullary tumor	40 (21.1)	18 (18.4)
Duodenal carcinoma	11 (5.8)	8 (8.2)
Other	6 (3.2)	0 (0.0)
Neuroendocrine tumor	8 (4.2)	6 (6.1)
Intraductal papillary mucinous neoplasm	16 (8.4)	11 (11.2)
Adenoma	2 (1.1)	5 (5.1)
Other	14 (7.4)	8 (8.2)
Unknown¶	4 (2.1)	2 (2.0)
Tumor size — median (IQR) mm	25 (17–33)	22 (15–30)

* IQR denotes interquartile range and PD, pancreatoduodenectomy.
† Conversion to open surgery was defined as the unplanned need to switch from a minimally invasive approach to laparotomy due to intraoperative challenges.
‡ Pancreatic texture was assessed intraoperatively and based on the surgeon's subjective evaluation.
§ Tumor size was defined as the largest diameter of the tumor in millimeters as measured by the pathologist.
¶ Unknown diagnosis refers to cases where histopathological findings were inconclusive or unavailable. Data were missing for soft/normal pancreatic texture (N=3), pancreatic duct diameter (N=7), type of pancreatic anastomosis (N=8), and tumor size (N=34).

No apparent differences in postoperative major morbidity or reintervention rates were observed between MIPD and OPD (Table 3). Other pancreatic surgery–related complication rates, such as rates of delayed gastric emptying, bile leakage, and postpancreatectomy hemorrhage, appeared to be comparable between groups. The rate of surgical site infection was 13% after MIPD versus 23% after OPD. The readmission rate appeared comparable between groups (30% vs. 26%). Among patients who underwent surgery for pancreatic ductal adenocarcinoma or distal cholangiocarcinoma, the radical (R0) resection rate and lymph node count appeared comparable between the groups (Table 3).

Data on the global health status and quality of life up to 6 months postoperatively are reported in the Supplementary Appendix, pages 27–30.

SUBGROUP AND SENSITIVITY ANALYSES

Outcomes of the per-protocol, as-treated, and sensitivity analyses are reported in Tables S7–S13. The additional

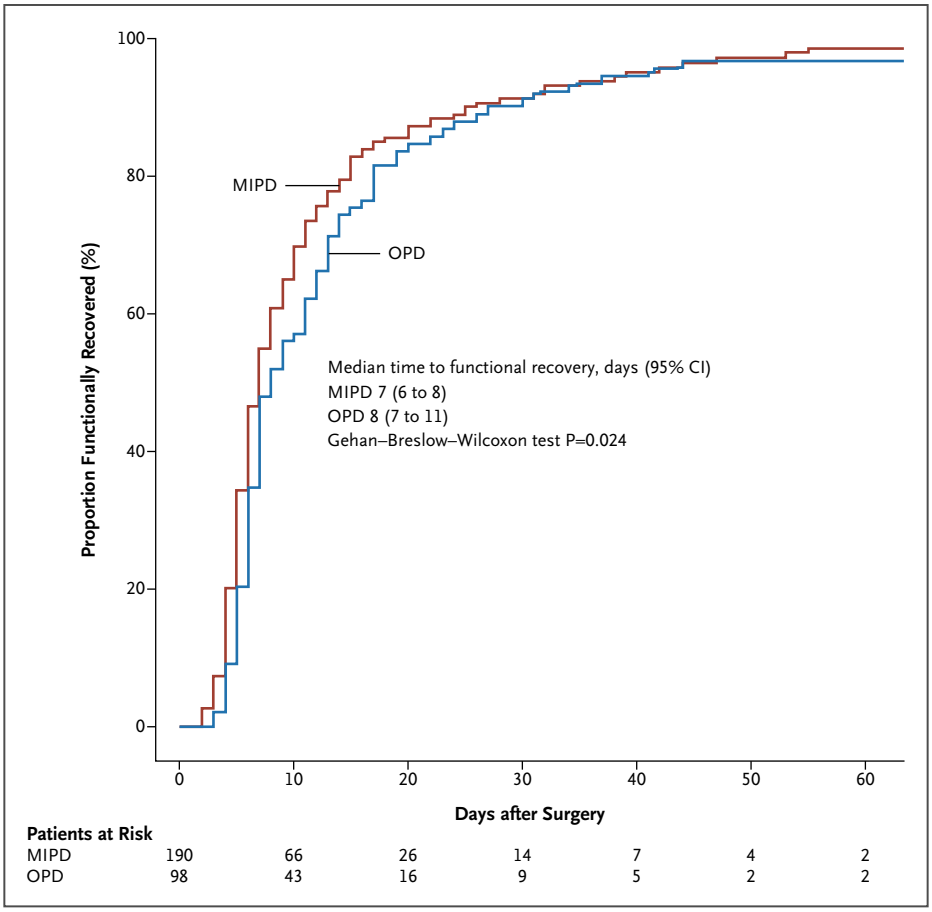

Figure 2. Kaplan–Meier Analysis of Time to Functional Recovery Following Minimally Invasive Pancreatoduodenectomy versus Open Pancreatoduodenectomy (Modified Intention-to-Treat Population).

Kaplan–Meier curves show the proportion of patients who functionally recovered over time. The median time to recovery was 7 days (95% confidence interval, 6 to 8) in the minimally invasive pancreatoduodenectomy group and 8 days (95% confidence interval, 7 to 11) in the open pancreatoduodenectomy group. The number at risk is shown below the *x*-axis. MIPD denotes minimally invasive pancreatoduodenectomy; OPD, open pancreatoduodenectomy; and CI, confidence interval.

per-protocol and as-treated analyses did not show differences in outcomes as compared with the primary modified intention-to-treat analyses. In patients operated on for pancreatic ductal adenocarcinoma, a higher CCI score was found after MIPD, without differences in specific complications or mortality rates. In the subgroup of patients with major complications, a lower CCI score was found after MIPD. An exploratory center-level analysis showed that CCI outcomes were broadly comparable between MIPD and OPD across participating centers (Table S19).

Discussion

This international, multicenter patient-blinded randomized trial comparing MIPD and OPD for resectable pancreatic and periampullary neoplasms confirmed the noninferiority of MIPD in terms of CCI (i.e., safety) up to 90 days after surgery.

MIPD was associated with 1-day faster TTFR, 2-day shorter hospital stays, a 13 percentage point reduction in postoperative pancreatic fistula occurrences, and a 10 percentage point reduction in surgical-site infection compared with OPD. Moreover, MIPD was associated with an increase in daily steps between postoperative days 14 and 38. No apparent differences were observed in reinterventions, readmissions, or quality of life between the two approaches within the 90-day postoperative period.

Our results support the hypothesis that MIPD, if performed in high-volume centers by experienced surgeons beyond the learning curve, may offer the advantage of

Table 3. Outcomes (Modified Intention-to-Treat Population).*

Outcome	Minimally Invasive PD (N=190)	Open PD (N=98)	Mean Difference or Relative Risk (95% CI)
Primary end point			
Comprehensive Complication Index†			
Mean±standard deviation	33.4±27.5	35.3±25.5	−1.9 (−8.5 to 4.7)
Median (IQR)	30.3 (8.7–48.1)	32.3 (11.8–52.7)	−2.4 (−11.3 to 6.5)
Secondary end points‡			
Operative time — median (IQR) minutes	339 (280–420)	296 (226–345)	43.0 (15.3 to 70.7)
Estimated operative blood loss — median (IQR) ml	175 (100–300)	300 (130–500)	−125 (−209 to −40)
Vascular resection — no. (%)	6 (3.2)	5 (5.1)	0.62 (0.19 to 1.98)
Histopathological R0 resection margin — no. (%)§,¶	46/89 (51.7)	23/40 (57.5)	0.90 (0.64 to 1.25)
Lymph node count — median (IQR) no.	16 (13–22)	17 (12–22)	−1.0 (−3.6 to 1.6)
Tumor positive nodes — median (IQR) no.	1 (0–4)	0 (0–2)	1.0 (−0.3 to 2.3)
Major morbidity (Clavien–Dindo grade ≥III) — no. (%)‖	92 (48.4)	51 (52.0)	0.93 (0.73 to 1.18)
IIIa	56 (29.5)	34 (34.7)	0.85 (0.60 to 1.21)
IIIb	15 (7.9)	8 (8.2)	0.97 (0.42 to 2.20)
IVa	9 (4.7)	6 (6.1)	0.77 (0.28 to 2.11)
IVb	3 (1.6)	1 (1.0)	1.55 (0.16 to 14.7)
V (death)	9 (4.7)	2 (2.0)	2.32 (0.51 to 10.5)
Complication-related mortality — no. (%)	8 (4.2)	2 (2.0)	2.06 (0.45 to 9.53)
Reintervention — no. (%)			
Radiologic	63 (33.2)	41 (41.8)	0.79 (0.58 to 1.08)
Endoscopic	38 (20.0)	22 (22.4)	0.89 (0.56 to 1.42)
Angiographic	11 (5.8)	8 (8.2)	0.71 (0.29 to 1.71)
Surgical	18 (9.5)	7 (7.1)	1.33 (0.57 to 3.07)
Unplanned ICU admission — no. (%)	21 (11.1)	14 (14.3)	0.77 (0.41 to 1.45)
If yes, total unplanned ICU stay — median (IQR) days	3.5 (2.0–20.5)	3.0 (2.0–17.0)	0.9 (−7.9 to 9.7)
Postoperative pancreatic fistula (B or C) — no. (%)	43 (22.6)	35 (35.7)	0.63 (0.44 to 0.92)
Bile leakage (B or C) — no. (%)	15 (7.9)	6 (6.1)	1.29 (0.52 to 3.22)
Delayed gastric emptying (B or C) — no. (%)	40/164 (24.4)	19/82 (23.2)	1.05 (0.65 to 1.70)
Postpancreatectomy hemorrhage (B or C) — no. (%)	15 (7.9)	10 (10.2)	0.77 (0.36 to 1.66)
Chyle leakage (B or C) — no (%)	5 (2.6)	3 (3.1)	0.86 (0.21 to 3.52)
Surgical-site infection — no. (%)	24 (12.6)	22 (22.7)	0.56 (0.33 to 0.94)
Superficial — no. (%)	12 (6.3)	13 (13.3)	0.48 (0.22 to 1.02)
Deep — no. (%)	5 (2.6)	3 (3.1)	0.85 (0.20 to 3.55)
Organ space — no. (%)	7 (3.7)	6 (6.1)	0.61 (0.21 to 1.81)
Pneumonia — no. (%)	22 (11.6)	9 (9.2)	1.26 (0.60 to 2.63)
Postoperative blood transfusion	36 (18.9)	19 (19.4)	0.97 (0.52 to 1.80)
Length of initial hospital stay — median (IQR) days	9 (6–15)	11 (7–20)	−2.0 (−4.7 to 0.7)
Total hospital stay <90 days — median (IQR) days	11 (7–23)	14 (8–27)	−2.6 (−6.1 to 0.9)
Readmission — no. (%)	57/189 (30.2)	25/96 (26.0)	1.16 (0.78 to 1.73)

* CI denotes confidence interval; ICU, intensive care unit; IQR, interquartile range; and PD, pancreatoduodenectomy.
† The Comprehensive Complications Index values range from 0 (no complications) to 100 (death) and are calculated using the sum of all complications weighted according to Clavien–Dindo grade. The P value equals 0.572 for the mean difference between the groups.
‡ Confidence intervals for secondary end points were not adjusted for multiple testing; therefore, no definite conclusions can be drawn from these data.
§ R0, microscopically negative resection margins (distance tumor to margin >1 mm); R1, microscopically positive resection margins (distance tumor to margin ≤1 mm). No R2 resections (macroscopically positive resection margins) were performed.
¶ Pancreatic ductal adenocarcinoma/distal cholangiocarcinoma pathological diagnosis (N=129).
‖ Clavien–Dindo grade III, complications requiring endoscopic or radiologic intervention or surgical intervention; Clavien–Dindo grade IV, complications leading to single-organ failure or multiorgan failure; Clavien–Dindo grade V, death. Data were missing for operative time (N=7), estimated operative blood loss (N=6), lymph node count (N=6), and tumor-positive nodes (N=6).

faster postoperative recovery without compromising patient safety in the short term. The findings of the DIPLOMA-2 trial contrast with those of the LEOPARD-2 trial, which was prematurely terminated for safety concerns.[5] The current DIPLOMA-2 trial mandated a threefold higher experience with MIPD for participating surgeons to mitigate the learning curve effect.[38,39] The minimum annual center volume of 30 MIPD procedures before participation in combination with 2:1 randomization safeguarded sufficient experience with MIPD during the trial.[40] The observed median annual center volume of 22 MIPD procedures among the participating centers confirms the impact of these design measures.

The associated 1-day reduction in TTFR in the MIPD group is modest and consistent with previous studies. Nevertheless, it does not seem unreasonable to speculate that the 3-day shorter overall hospital stay could be useful, especially in regions and countries with nursing staff shortages and, consequently, pressures on hospital bed capacity. In contrast, the single-center phase 2 EUROPA trial from Germany did not demonstrate a benefit in TTFR with robotic MIPD as compared with OPD.[10] Moreover, the primary end point, as measured by CCI score, did not differ between the groups in the EUROPA trial, which also reported higher rates of major (grade B or C) pancreatic surgery–specific complications after robotic MIPD. As noted by the authors, and suggested by the 23% conversion rate, that trial was performed during the early stages of the surgeons' learning curve.[41] A second randomized trial on robotic MIPD from China reported that the sole benefit for robotic MIPD was a median 2.5-day shorter hospital stay.[11] Therefore, the DIPLOMA-2 trial reports multiple advantages of (robotic) MIPD over OPD, highlighting the importance of center experience and volume. Such experience is ideally acquired following a structured training program to minimize and shorten the learning curve.[39]

The vast majority (89.5%) of MIPD procedures in DIPLOMA-2 were performed robotically, which is in line with the ongoing strong shift from laparoscopic to robotic pancreatic surgery worldwide.[6] In addition, during the trial, all three centers that initially performed high-volume laparoscopic MIPD surgery switched to robotic MIPD. Therefore, only a small proportion of laparoscopic MIPD procedures was included. This also means that no conclusion can be drawn regarding the safety of laparoscopic MIPD in our trial. In addition to the LEOPARD-2 trial, four other randomized trials compared laparoscopic MIPD with OPD. Two single-center trials from India and Spain reported shorter hospital stays with comparable or lower complication rates after laparoscopic MIPD.[7,8] Furthermore, two large multicenter trials from the same research group from China reported similar postoperative outcomes for laparoscopic pancreaticoduodenectomy compared with OPD.[9,42] None of these trials reported superior results of MIPD, as compared with OPD.

Notably, the association between MIPD and lower rates of postoperative pancreatic fistula, lower rates of surgical site infection, and increased daily activity observed after robotic MIPD compared with OPD in the current trial suggests potential benefits of MIPD, which have not been reported in previous randomized trials on MIPD versus OPD. The lower fistula rate after MIPD was unexpected but observed across most participating centers. All surgeons met strict volume and experience thresholds (≥60 MIPD and ≥60 OPD procedures), and conversion rates were evenly distributed across centers, which makes variation in surgical expertise as an explanation for this finding unlikely. Stratified analysis indicated comparable postoperative pancreatic fistula risks between groups. It is important to note that patients eligible for MIPD typically have a high pancreatic fistula risk, which includes a challenging pancreatic reconstructive phase. We speculate that, in these patients with small pancreatic ducts, the enhanced visualization and dexterity offered by the robotic platform may facilitate a more precise anastomosis. Further in-depth analyses and prospective studies are required to critically assess this potential advantage of MIPD. Similarly, the lower levels of blood loss rates despite longer operative time are also interesting; less blood loss and a shorter operative time in the MIPD group were reported in the trial from China, whereas the EUROPA trial reported no difference in blood loss and longer operative times.[10,11]

The overall 90-day mortality rate in the DIPLOMA-2 trial was 4.7% for MIPD versus 2.0% for OPD, with no apparent differences in reinterventions or intensive care unit admissions between the groups. The most common cause of death was postoperative pancreatic fistula, whereas no intraoperative adverse events resulted in patient death. The high rate of postoperative pancreatic fistula in the selected patients undergoing MIPD confirms the ongoing relevance of auditing the safe introduction of MIPD as advised by international guidelines.[40]

Surgical trials can be complex, often involving both methodological and practical challenges. In the DIPLOMA-2 trial, patient blinding up to postoperative day 5 was successfully implemented, minimizing bias in early activity assessment. The blinding of the laparotomy wound in patients who underwent OPD may even have positively influenced TFFR in these patients, as well as reduced pain sensation.

A frequent criticism of surgical randomized trials, particularly when comparing novel with conventional interventions, is the potential imbalance in surgical expertise among surgeons. Such disparities in experience can skew outcomes, especially regarding safety and complications. The DIPLOMA-2 trial specifically addressed this through measures safeguarding both sufficient surgeon experience and center volume.

The results of this trial should be interpreted considering several limitations. First, the CCI score is quite difficult to measure because lower-grade complications are quite common in patients after pancreatoduodenectomy, and scoring may involve heterogeneity due to interpretation. We tried to minimize heterogeneity by creating an instruction manual for scoring complications (Table S1), performing an on-site cross-check, and conducting two blinded adjudication committee meetings. Second, as this was a pragmatic trial, procedures were not standardized. This means that differences in drain management, pain management, postoperative feeding protocols, and other factors between centers did exist. However, in each center, one postoperative protocol was used for patients undergoing both MIPD and OPD. Third, the results of this trial apply to high-volume centers with experienced surgeons. Caution should be exercised when extrapolating these findings to lower-volume centers or settings with less-specialized surgeons. Both the evidence-based Miami[40] and Brescia[43] guidelines state that a center should perform at least 20 MIPD procedures per year. To select 20 patients for MIPD, a center should probably perform at least 40–50 pancreatoduodenectomies per year. The higher (i.e., 60) center volume cutoff value in this trial was chosen to maintain sufficient experience with MIPD during the trial, as a third of patients were randomized to OPD. Fourth, our trial was focused on a specific subset of the patients undergoing pancreatoduodenectomy, namely those without vascular contact and with a BMI of less than 35. Further studies are warranted to evaluate the safety and efficacy of MIPD in patients with a BMI above 35 and vascular involvement. Fifth, patients with pancreatic ductal adenocarcinoma only form a minority in this trial (29.2%); for this reason, the DIPLOMA 2×2 trial is currently ongoing to answer questions regarding the oncological efficacy of (robotic) MIPD versus OPD (ISRCTN27483786). Sixth, a limitation of this trial is the relatively short follow-up period, which precludes definitive conclusions about long-term oncological outcomes; future trials with extended follow-up are needed to determine whether MIPD and OPD differ in cancer-related survival and recurrence. Strengths of this trial include the international multicenter design, the blinding, the experience thresholds for participating surgeons and centers, and the patient activity measurements.

Conclusion

In conclusion, the DIPLOMA-2 trial demonstrated the noninferiority of MIPD to OPD regarding CCI scores in patients with a primary resectable pancreatic and periampullary neoplasm. In addition, MIPD was associated with a modest benefit in terms of TTFR.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

The medical ethics review committee of the Amsterdam University Medical Center, location Academic Medical Center (Amsterdam, the Netherlands; NL77750.018.21) and Provincial Ethic Committee Brescia (Brescia, Italy; NP4916) approved the trial protocol. The trial was registered with the identification number ISRCTN27483786. Patients could only participate if written informed consent was provided.

On reasonable request, deidentified data collected for the DIPLOMA-2 trial, the trial protocol, and the informed consent form can be made available. Please contact the principal investigators, Mohammad Abu Hilal and Marc Besselink. All requests should fulfill the following access criteria: all research is conducted with the DIPLOMA-2 trial investigators' support, after approval of a proposal by the scientific committee of the European Consortium on Minimally Invasive Pancreatic Surgery research committee, and with a signed data access agreement. The DIPLOMA-2 trial investigators will be allowed to approve all research performed with the shared data.

Intuitive Surgical (Switzerland) financially supported the investigator-initiated DIPLOMA-2 trial (reference number I). The funder had no influence on the trial design and will not have influence on data collection, interpretation of data, manuscript development, or the decision to publish.

We would like to acknowledge all surgeons and researchers from the European Consortium on Minimally Invasive Pancreatic Surgery who participated in the DIPLOMA-2 trial. We thank Dr. Thomas van Gulik, Dr. John Primrose, Dr. Peter van de Ven, Dr. Michael Ghidini, Dr. Cees Verhoef, and Dr. Andrew Cook for their participation in the data safety monitoring board; Dr. Pieter Tanis (Erasmus University Medical Center, Rotterdam, the Netherlands) and Dr. Antonino Spinelli for their participation as independent experts; and all other collaborators for their dedication and efforts throughout the trial.

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