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

J. van Hilst, MD, MSc[1], T. de Rooij, MSc[1], S. Klompmaker, MD[1], M. Rawashdeh, MD[2], F. Aleotti, MD[3], B. Al-Sarireh, MD, PhD[4], A. Alseidi, MD[5], Z. Ateeb, MD[6], G. Balzano, MD[3], F. Berrevoet, MD, PhD[7], B. Björnsson, MD, PhD[8], U. Boggi, MD[9], O.R. Busch, MD, PhD[1], G. Butturini, MD, PhD[10], R. Casadei, MD, PhD[11], M. del Chiaro, MD, PhD[6], S. Chikhladze, MD[12] F. Cipriani, MD[2], R. van Dam, MD, PhD[13], I. Damoli, MD[14], S. van Dieren, PhD[1], S. Dokmak, MD[15], B. Edwin, MD, PhD [16], C. van Eijck, MD, PhD[17], J.M. Fabre, MD, PhD[18], M. Falconi, MD[3], O. Farges, MD, PhD[15], L. Fernández-Cruz, MD[19], A. Forgione, MD, PhD[20], I. Frigerio, MD[10], D. Fuks, MD, PhD[21], F. Gavazzi, MD[22], B. Gayet, MD, PhD[21], A. Giardino, MD[10], B. Groot Koerkamp, MD, PhD[17], T. Hackert, MD[23], M. Hassenpflug, MD[23], I. Kabir, MD[24], T. Keck, MD[25], I. Khatkov, MD, PhD[26], M. Kusar, MD[27], C. Lombardo, MD[9], G. Marchegiani, MD[14], R. Marshall, MD[5], K.V. Menon, MD, PhD[28], M. Montorsi, MD[22], M. Orville, MD[15], M. de Pastena, MD[14], A. Pietrabissa, MD[29], I. Poves, MD, PhD[30], J. Primrose, MD, PhD[2], R. Pugliese, MD[20], C. Ricci, MD[11], K. Roberts, MD, PhD[31], B. Røsok, MD, PhD[16], MA. Sahakyan, MD, PhD[16], S. Sánchez-Cabús, MD, PhD[19], P. Sandström, MD, PhD[8], L. Scovel, MD[5], L. Solaini, MD[32], Z. Soonawalla, Ms, FRCS[24], F.R. Souche, MD[18], R.P. Sutcliffe, MD[31], G.A. Tiberio, MD[32], A. Tomazic, MD, PhD[27], R. Troisi, MD, PhD[7], U. Wellner, MD[25], S. White, MD[33], U.A. Wittel, MD[12], A. Zerbi, MD[22], C. Bassi, MD[14], M.G. Besselink, MD, MSc, PhD[1*], M. Abu Hilal, MD, PhD[2*] for the European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS)

* Principal investigators and shared senior authors

1. Department of surgery, Cancer Center Amsterdam, Academic Medical Center, Amsterdam, the Netherlands
2. Department of surgery, Southampton University Hospital NHS Foundation Trust, Southampton, United Kingdom
3. Department of surgery, San Raffaele Hospital, Milan, Italy
4. Department of surgery, Morriston Hospital, Swansea, United Kingdom
5. Department of surgery, Virginia Mason Medical Center, Seattle, United States
6. Department of surgery, Karolinska Institute, Stockholm, Sweden
7. Department of general and HPB surgery and liver transplantation, Ghent University Hospital, Ghent, Belgium

8. Department of surgery, Linköping University, Linköping, Sweden

9. Department of surgery, Universitá di Pisa, Pisa, Italy

10. Department of surgery, Pederzoli Hospital, Peschiera, Italy

11. Department of surgery, S. Orsola-Malpighi Hospital, Bologna, Italy

12. Department of surgery, Universitätsklinikum Freiburg, Freiburg, Germany

13. Department of surgery, Maastricht University Medical Center, Maastricht, the Netherlands

14. Department of surgery, Pancreas Institute, Verona University Hospital, Verona, Italy

15. Department of surgery, Hospital of Beaujon, Clichy, France

16. Department of surgery, Oslo University Hospital and Institute for Clinical Medicine, Oslo, Norway

17. Department of surgery, Erasmus MC, Rotterdam, the Netherlands

18. Department of surgery, Hopital Saint Eloi, Montpellier, France

19. Department of surgery, Hospital Clínic de Barcelona, Barcelona, Spain

20. Department of surgery, Niguarda Ca' Granda Hospital, Milan, Italy

21. Department of surgery, Institut Mutualiste Montsouris, Paris, France

22. Department of surgery, Humanitas University Hospital, Milan, Italy

23. Department of surgery, Heidelberg University Hospital, Heidelberg, Germany

24. Department of surgery, Oxford University Hospital NHS Foundation Trust, Oxford, United Kingdom

25. Clinic for surgery, UKSH Campus Lübeck, Lübeck, Germany

26. Department of surgery, Moscow Clinical Scientific Center, Moscow, Russian Federation

27. Department of surgery, University Medical Center Ljubljana, Ljubljana, Slovenia

28. Department of surgery, King's College Hospital NHS Foundation Trust, London, United Kingdom

29. Department of surgery, University hospital Pavia, Pavia, Italy

30. Department of surgery, Hospital del Mar, Barcelona, Spain

31. Department of surgery, University Hospital Birmingham, Birmingham, United Kingdom

32. Surgical clinic, Department of clinical and experimental sciences, University of Brescia, Brescia, Italy

33. Department of surgery, The Freeman Hospital Newcastle Upon Tyne, Newcastle, United Kingdom

Corresponding authors:

Mohammed Abu Hilal, MD PhD FRCS FACS

During review process:
Jony van Hilst, MD, MSc

Southampton University Hospital NHS
Foundation Trust
Tremona Road, SO16 2YD
Southampton, UK
Tel: +44-23-8077-7222
Email: abuhilal9@gmail.com

Marc G Besselink, MD, MSc, PhD
Academic Medical Center
Department of surgery, G4-196
PO BOX 22660
1100 DD Amsterdam
The Netherlands
+3125662558
m.g.besselink@amc.nl

Academic Medical Center
Department of surgery, G4-136
PO BOX 22660
1100 DD Amsterdam
The Netherlands
+3125661388
j.vanhilst@amc.nl

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Mini-abstract

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

Structured Abstract

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

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

Methods: A pan-European propensity score matched study including patients who underwent MIDP (laparoscopic or robot-assisted) or ODP for PDAC between January 1st, 2007 and July 1st, 2015. MIDP patients were matched to ODP patients in a 1:1 ratio. Main outcomes were radical (R0) resection, lymph node retrieval, and survival.

Results: In total, 1212 patients were included from 34 centers in 11 countries. Out of 356 (29%) MIDP patients, 340 could be matched. After matching, the MIDP conversion rate was 19% (n=62). Median blood loss (200mL [60–400] vs. 300mL [150–500], *P*=0.001) and hospital stay (8 [6-12] vs. 9[7-14] days, *P*<0.001) were lower after MIDP. Clavien-Dindo grade ≥3 complications (18% vs. 21%, *P*=0.431) and 90-day mortality (2% vs. 3%, *P*>0.99) were comparable for MIDP and ODP, respectively. R0 resection rate was higher (67% vs. 58%, *P*=0.019), whereas Gerota's fascia resection (31% vs. 60%, *P*<0.001) and lymph node retrieval (14 [8-22] vs. 22 [14-31], *P*<0.001) were lower after MIDP. Median overall survival was 28 [95% CI 22-34] vs. 31 [95% CI 26 – 36] months (*P*=0.929).

Conclusion: Comparable survival was seen after MIDP and ODP for PDAC, but the opposing differences in R0 resection rate, resection of Gerota's fascia and lymph node retrieval strengthen the need for a randomized trial to confirm the oncological safety of MIDP.

Introduction

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

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

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

Methods

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

Design and patients

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

Definitions

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

Data collection

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

Matching

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

Statistical analyses

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

Results

Participating centers

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

Total cohort

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

Matched cohort

Of all MIDPs, 96% could be matched successfully to an ODP control. As shown in Table 1 (matched cohort), significant differences in baseline characteristics were no longer present after matching. Table 2 (matched cohort) shows intra-operative outcomes. Conversion from MIDP to ODP occurred in 62 patients (19%). Median blood loss was lower during MIDP (200 [60 – 400] vs. 300 [150 – 500] mL, P=0.001). Splenectomy (93% vs. 97%, P=0.01), resection of Gerota's fascia (31% vs. 60% patients, P<0.001) and vascular resections (6% vs. 11%, P=0.012) were performed less frequently during MIDP compared with ODP. An adrenal gland resection was more often performed during MIDP (11% vs. 6%, *P*=0.029). Table 3 (matched cohort) shows that the median lymph node retrieval was less during MIDP (14 [8-22] vs. 22 [14-31] nodes, *P*<0.001), the lymph node ratio was comparable between both groups (0.06 [0 – 0.18] vs 0.08 [0.17], *P*=0.403) whereas the R0 resection rate was higher in the MIDP group (67% vs. 58%, *P*=0.019). Lymphovascular invasion (56% vs. 71% patients, *P*<0.001) and perineural tumor invasion (63% vs. 75% patients, *P*<0.001) were less often seen in the MIDP group. No statistical significant differences in postoperative complications between MIDP and ODP were seen (Table 4, matched cohort). MIDP was associated with shorter postoperative hospital stay compared with ODP (8 [6-12] vs. 9 [7-14] days, *P*<0.001). The median follow-up time was 13 (range: 0 – 84) months. Median overall survival was comparable for both procedures (28 [95% CI 22 – 34] vs. 31 [95% CI 26 – 36] months, *P*=0.774) The hazard ratio was 1.025 (95% CI 0.75 – 1.27) for MIDP compared with ODP (*P* = 0.85).

Sensitivity analyses

No difference in pathology outcomes and survival were seen after excluding patients who received neoadjuvant therapy (Supplementary Table 1). Excluding patients after distal pancreatectomy without splenectomy did not alter radicality and survival outcome (Supplementary Table 2) whereas the differences in number of retrieved lymph nodes remained (MIDP 14 (8-22) vs. ODP 22 (15-31), *P* <0.001).

Effect of time

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

Discussion

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

Three matched cohorts specifically focusing on MIDP vs. ODP for patients with PDAC have been published. One study in 102 patients used propensity score matching[25] and two studies in 51 and 93 patients used case matching.[26,27] Reduced length of hospital stay after MIDP was reported in two studies[25,27] and less intraoperative blood loss in one study[27]. As in the current study, none of the previously published studies reported a difference in postoperative complication rates. Conversion rate was reported in two studies and was slightly lower than reported in the current study (12% and 17% vs. 19% (Table 2).[26,27] This slightly higher rate of conversions could possibly be explained by the inclusion of procedures performed during the learning curve. Due to a different moment of introduction of MIDP in the participating centers a decrease in conversion rate over time was not seen (Supplementary Table 3).

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

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

The presence of perineural invasion was only reported in one matched cohort study and in contrast to the current study no statistical significant difference between MIDP and ODP was seen.[27] Lymphovascular invasion was not reported by any matched study

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

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

Despite the clear strengths of this study, some limitations have to be discussed. First, most data were collected retrospectively which could have possibly led to underreporting of postoperative outcomes such as complications. Second, missing data were present. However, no differences between the baseline characteristics before and after imputation were present (Supplementary Table 1). For optimal transparency, all missing variables were reported and data should be interpreted in perspective to the degree of missing data. Third, despite our attempt to minimize the influence of treatment allocation bias, by applying propensity score matching, treatment allocation bias may still have influenced outcomes in the matched cohort. Although we managed to correct for differences in baseline variables, the difference in lymphovascular and perineural tumor invasion between the MIDP and ODP group (Table 3, matched cohort) suggests that less aggressive tumors have been selected for the minimally invasive approach. The absence of these factors are associated with better survival in the literature,[26,34] and as a consequence, this could have influenced the results. On the other hand, lymph node ratio was comparable between both groups. Fourth, this study was mainly an European effort and a median BMI of 25 was reported, which is lower compared to, for example, the median BMI in the USA. Consequently, this difference could influence the applicability of the results of the current studies to non-European countries. Attempts should be made to include centers from outside of Europe in further studies. Lastly, the possible variation in surgical techniques and pathology assessment and reporting between centers represent a serious challenge. The influence of these variations on the results remain unknown and could be limited due to the use of the same approach in MIDP and ODP at a given center. Efforts to develop standardized surgical technique, pathology assessment and pathology reporting should be made and the influence of implementation of these guidelines should be studied.

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

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Collaborators

G Sergeant, department of surgery, Jessa Ziekenhuis, Hasselt, Belgium; S Berti, department of surgery, St. Andrea Hospital, La Spezia, Italy.

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