Outcomes after minimally-invasive or open pancreatoduodenectomy in high-volume centers; a Pan-European retrospective propensity-score matched cohort study

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Abbreviations
ASA American Society of Anesthesiologists
CDC Center for Disease Control and Prevention
DGAV Deutschen Gesellschaft für Allgemein- und Viszeralchirurgie
DPCA Dutch pancreatic cancer audit
E-AHPBA European-African Hepato- Pancreato- Biliary- Association
E-MIPS European consortium on Minimally-Invasive Pancreatic Surgery
HIPAA Health Insurance Portability and Accountability Act
IQR Interquartile range
ISGPF International Study Group on Pancreatic Fistula
ISGPS International Study Group on Pancreatic Surgery
LPD Laparoscopic pancreatoduodenectomy
MIPD Minimally-invasive pancreatoduodenectomy
OPD Open pancreatoduodenectomy
PD Pancreatoduodenectomy
PDAC Pancreatic ductal adenocarcinoma
SD Standard deviation
StuDoQ Studien-, Dokumentations- und Qualitätszentrum
1. Protocol Abstract

RATIONALE: Minimally-invasive pancreateoduodenectomy (MIPD), either laparoscopic or robot-assisted, has been suggested as a valuable alternative to open pancreateoduodenectomy (OPD). The generalizability of the current literature is, however, unknown since randomized studies are lacking, and current data are published from few, very high volume centers and selection bias with a lack of case-matched series. International studies are lacking completely.

OBJECTIVE: To compare outcomes of MIPD versus open pancreateoduodenectomy (OPD), in high-volume European pancreas centers (>10 MIPDs per year, total >20 PDs per year).

METHODS: A retrospective multicenter propensity-score matched cohort study including all consecutive patients who underwent MIPD (or MI total pancreatectomy) between January 2012 and December 2016, for pancreatic head, bile duct, or duodenal cancer or cysts except chronic pancreatitis. Predefined electronic case report forms will be disseminated amongst participating centers. Participants are responsible for their own data collection. Matching of MIPD cases (collected from participating centers) to OPD controls (extracted from Dutch and German national registries) will be based on propensity scores determined by logistic regression including preoperative variables: year of surgery, demographics, BMI, ASA, comorbidities, tumor size, tumor etiology (diagnosis), and multivisceral resection. Primary outcome is 90-day major morbidity (Clavien-Dindo ≥ 3a). Secondary outcomes are 90-day postoperative events including: pancreatic fistula, length of hospital stay, R0 (microscopically negative) resection margin, malignant lymph node ratio, days to adjuvant therapy and overall survival.

STRENGTHS: This multicenter study will involve a large sample of patients treated in high-volume European centers, which will allow for the assessment of post-learning curve application of MIPD across Europe. The potential effects of confounding by case selection will be mitigated by propensity-score analysis. The assessment of outcomes will be based solely on highly practiced surgeons and high-volume institutions.

LIMITATIONS: General limitations associated with retrospective studies are selection bias, information bias and follow-up bias. Specific limitations of this study include time-dependent treatment bias, between-center heterogeneity in: data collection and reporting, execution of the procedure, surgical case selection, and postoperative management. Moreover, the results of this study will only be applicable to high-volume centers.

PLANNING: The study design phase will be completed by December 2016, after which data collection will start in January 2017 and will last for 4 months. Data-analysis and manuscript completion are expected around mid-2017.
2. Introduction

Minimally-invasive pancreatoduodenectomy (MIPD) has been regarded as a valuable alternative to the existing treatment options for patients with pancreatic head, bile duct, or duodenal lesions.1-6 In a meta-analysis of retrospective comparative studies between MIPD and open pancreatoduodenectomy (OPD), outcomes favoring MIPD included reduced intraoperative blood loss in mL (mean weighted difference [WMD] -348.72, 95% confidence interval [CI] -615.71, -153.72), lower odds of R1 resection (odds ratio [OR] 0.70, CI 0.50, 0.99), lower odds of delayed gastric emptying (OR 0.62, CI 0.46, 0.82), and reduced lengths of stay in days (WMD -3.14, CI 4.71, 1.56).2

Despite promising results by early adapting centers, the retrospective nature of the published literature results in three main concerns about the quality of the evidence. The single center set-up of most studies raises questions of generalizability and the large proportion of low-volume centers may have led to suboptimal outcomes of MIPD in comparison to OPD. The lack of randomization or matching may have led to confounding by patient selection.

The effect of volume on outcomes after pancreatic surgery has been studied previously, indicating better outcomes at annual case volumes exceeding 40.7 Three recent registry studies have reported significant beneficial effects of hospital volume on outcomes after MIPD, however with substantial heterogeneity of the high-volume definition.8-10 Three reports comparing OPD versus MIPD have originated from institutions with an annual case volume exceeding 19.11-13 However, only one of these reports has performed a case-matched analysis to mitigate the effects of selection bias.13

One single center randomized controlled trial (RCT) comparing laparoscopic versus open pancreatoduodenectomy for benign and malignant lesions has recently been completed in India (NCT02081131). Currently, one monocenter RCT in Barcelona (PADULAP; ISRCTN93168938) and one multicenter RCT in the Netherlands (LEOPARD-2: NTR5689) are ongoing. Outcomes of multicenter studies may potentially have superior external generalizability as they more closely reflect clinical practice. Although randomization resolves the issue of selection bias, an international, pan-European trial may be difficult to perform. Moreover, results are not expected within the next two years thus a more urgent need for high-quality evidence on MIPD persists.

We intent to perform a retrospective multicenter propensity-score matched cohort study in high-volume centers (>10 MIPDs per year and overall >20 PDs per year) to provide an assessment of the implementation of MIPD (including MI total pancreatectomy) and the outcomes after MIPD versus OPD. The evidence gained by this study will provide real-life outcomes of MIPD amongst high-volume pancreatic centers. We hypothesize that MIPD is associated with equivalent morbidity and mortality compared to OPD, when performed in such high-volume centers, but with a shorter hospital stay.
3. **Specific aims**

1. To perform a propensity-score matched cohort analysis of MIPD cases collected at participating E-AHPBA centers versus OPD cases performed at high-volume centers (>20 PDs annually), extracted from the Dutch Pancreatic Cancer Audit (DPCA) and the German Studien-, Dokumentations- und Qualitätszentrum (StuDoQ|Pancreas) registry established by the German Society for General and Visceral Surgery (DGAV).

2. To assess current implementation and standards of care associated with MIPD across high-volume E-AHPBA member centers (>10 MIPDs annually) across Europe.

4. **Methods**

This is a pan-European retrospective multicenter propensity-score matched cohort study of MIPD versus OPD performed in participating high-volume centers, endorsed by the scientific committee of the E-AHPBA.

4.1 **Patients and design**

All consecutive patients who underwent elective MIPD (laparoscopic or robot-assisted; pancreatoduodenectomy or total pancreatectomy) between January 1st 2012 and December 31st 2016 will be retrieved. However, each center is encouraged to also include their first MIPD cases. Country and center of origin will be blinded to maintain anonymity on outcomes. In sensitivity-analyses, outcomes will be grouped based on center characteristics, such as volume. All indications for MIPD will be included, only patients will be excluded in case of a history of chronic or acute pancreatitis as only indication. Minimally-invasive total pancreatectomy cases will be included because in the minimally-invasive approach they also include a Whipple procedure.

4.2 **Definitions**

Preoperative variables include the typical baseline characteristics, such as age, sex, BMI. But also comorbidities (Charlson comorbidity index), past surgical history, CT/MRI-scan information (vascular/other organ involvement), and ASA-classification. Postoperative complications are scored and classified using the Clavien-Dindo classification of surgical complications\(^\text{14}\). Major complications are defined as Clavien-Dindo grade 3a or higher. The definitions of the recommended International Study Group on Pancreatic Surgery (ISGPS) and International Study Group on Pancreatic Fistula (ISGPF) are used to score postoperative pancreatic fistula, delayed gastric emptying, post pancreatectomy hemorrhage, and bile leakage.\(^\text{15-17}\) Surgical site infection is defined using the Center for Disease Control and Prevention (CDC) definition.\(^\text{18}\) Resection margins, , are categorized according to the Royal College of Pathologists\(^\text{19}\) definition and classified into R0 (distance margin to tumor ≥ 1mm), R1 (distance margin to tumor < 1mm) and R2 (macroscopically positive margin). All complications (minor
or major) occurring during the initial hospitalization are recorded. Complications requiring readmission and/or reoperation are recorded up to 90-days postoperatively. See Appendix 1 for all variables recorded.

4.3 Data collection

Current implementation and standard of care
A survey (Google™ Survey, Mountain View, CA, USA) will be sent to all participants, inquiring about current implementation of minimally invasive surgery, annual case volumes, and standards of care at the participant institution. This information may be used in the analyses, as a base for sub group or sensitivity analyses.

Minimally-invasive pancreatoduodenectomy
Each participating center will appoint one dedicated local study coordinator, responsible for all communication with the chief study coordinators (SK and JH). Each center will subsequently receive a login codes and passwords for the on-line electronic case report form (eCRF) environment (CASTOR®, CIWIT B.V., Amsterdam). Each data collector will receive a separate login account of which all activity can be monitored by the chief study coordinators. All MIPD (and MI total pancreatectomy) cases need to be validated by the local study coordinator prior to finalization and use in the final analysis. All edit and audit trails will be logged in conformity with Good Clinical Practice (GCP) guidelines.

Open pancreatoduodenectomy
OPD control patients will be extracted from two national surgical registries: The Dutch DPCA and the German DGAV StuDoQ|Pancreas. The DPCA is a prospectively maintained registry, with mandatory participation for all 17 Dutch pancreatic surgery centers. The DPCA registry contains all pancreatic resections performed in the Netherlands from 2005 up to the present. The DGAV StuDoQ|Pancreas registry contains all pancreatic resections of participating centers in Germany since its start in September 2013. At present, an estimated 15-20% of all pancreatic resections in Germany are documented in the registry. Participation will be mandatory for pancreatic surgery centers certified by the DGAV (German Society for General and Visceral Surgery) in 2017. As of end 2016, the Dutch DPCA and German DGAV StuDoQ|Pancreas can be merged to a set of 95 common clinical variables/parameters including baseline, operation, outcome, histopathologic, oncologic and follow-up parameters.

4.4 Primary and secondary endpoints
The Primary outcome is 90-day major morbidity (Clavien-Dindo ≥ 3a). The three most important secondary outcomes are 90-day mortality, grade B/C pancreatic fistula rate, and length of hospital stay (day of surgery to discharge). Other secondary outcomes are intra-operative outcomes (incl. blood loss, operative time and conversion), R0 resection margin (microscopically radical resection
margin, according to the Royal College of Pathologists definition\textsuperscript{19}, malignant lymph node ratio, and overall survival.

4.5 Ethics
Waived IRB approval from the Academic Medical Center ethics review committee was obtained. All data will be collected encoded, minimizing potential patient identifiers, using a GCP-certified eCRF environment\textsuperscript{20}. Participating centers will be asked to link the patient’s local medical record numbers to a pseudonym study ID (center acronym_MIPD_random-patient-ID). This information will be stored locally at the responsibility of participating centers. In case additional data extraction is needed, participating centers may be asked to re-identify patients locally based on the patient study ID. All aspects of the project will be handled in accordance with the STROBE guidelines\textsuperscript{21} on reporting of observational studies (see appendix 3 for checklist).

4.6 Statistical analyses
All data analyses will be performed by SK and JH and crosschecked by a dedicated statistician from the German DGAV StuDoQ|Pancreas project.

Reporting of data
Data will be analyzed using IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Orchard Road Armonk, New York, US), STATA version 14.1 (StataCorp LP, College Station, Texas, US), or R’s programming environment. Student’s t, Mann Whitney U, Chi-square, or Fisher’s exact tests will be used as appropriate. Categorical data will be presented as proportions, continuous data will be presented as either mean and standard deviation or median and inter-quartile-range as appropriate. Alpha <0.05 will be used to indicate statistical significance. Missing data will be resolved by multiple imputation wherever appropriate. All analyses will be performed based on intention to treat.

Propensity-scored matching
Both cohorts (MIPD and OPD) will be matched using propensity-score case-matching according to the recommendations reported by Lonjon et al.\textsuperscript{22}. Matching will be done on at least 1:1 ratio without replacement, with a conservative caliper width of 20\% of the standard deviation of the log of propensity score, based on covariates such as age, sex, body-mass-index (BMI), American Society of Anesthesiologists (ASA) classification\textsuperscript{23}, tumor t-stage\textsuperscript{24}, and multivisceral resection. At least one sensitivity analyses will be performed to assess possible differences between laparoscopic and robot-assisted surgery.

Survival analysis
After confirmation of proportional hazards, a COX-model will be constructed to assess survival. A stratified analysis based on tumor histology type, adjusting for baseline differences, will be performed to compare survival between MIPD and OPD.
Sample size calculation

Considerable heterogeneity exists in published literature regarding the registration of and reporting on morbidity after pancreatoduodenectomy. The most recent systematic review (both matched and unmatched studies) showed no difference in any complications between MIPD and OPD (OR 1.03, 95% CI 0.79–1.35, p = 0.83, I² = 33 %)\textsuperscript{25}. An older registry study from the United States did reveal a difference in uncategorized postoperative complications (46 vs. 39.4 %; p = 0.001) in favor of MIPD\textsuperscript{8}. When we performed a pooled meta-analysis on 3 case-matched studies on MIPD versus OPD, collected during a recent systematic review performed by our own team\textsuperscript{1}, we found no significant relative risk difference (RR 1.43, CI 0.86–2.37, p=0.99, I² = 0%) for major morbidity (Clavien-Dindo ≥ 3a), at a case-weighted mean proportion of 9.2%. Due to concerns of underreporting in the current literature, we estimated the real rate of 90-day postoperative major morbidity to be around 20%.

For the current study, a non-inferiority sample size estimation yielded that if at least 198 patients are included in each cohort, this will result in a 80% power to detect inferiority based on a 90-day major morbidity rate of 20%, with a non-inferiority limit of 10% in independent cohorts, and an alpha level of 0.05.

5. Authorship and publication policy

Authorships will be based on international guidelines. Centers providing at least 15 MIPD cases will be eligible for 1 authorship position, with eligibility for 2 authorship positions when providing at least 30 MIPD cases. All collaborating centers can include 1 author as formal ‘collaborator’ on the project. Centers with at least 30 cases can include 1 additional ‘collaborator’ for data-collection.

Each participating center will decide internally which local investigator will be listed as co-author. The study coordinators (SK and JH) will be the first and second authors. The last authorship positions are reserved for the 4 principal investigators (DF, TK, UB, MB). All other authors will be listed in alphabetical order. Any publication, presentation or abstract on collected data will be delegated to all authors. Each center keeps ownership of their own data and additional reports on data collected will only be conducted in case of written author permission. All participating authors can suggest alterations to the study design or additional analyses. The 5 principal investigators together with the 2 study coordinators constitute the steering committee of the project.
6. References


Appendix 1

Baseline and outcome variables

See separate Excel workbook.
Appendix 2

Standard of care survey

DATA COLLECTION QUESTIONS

1. Please provide the name and contact details of the local study coordinator at your institution:
   a. First name
   b. Initial(s)
   c. Last name
   d. Academic title/degree
   e. Job title
   f. Institution name
   g. Department name
   h. Institution address (street + number)
   i. City
   j. Postal code
   k. Province
   l. Country
   m. Email address
   n. Phone number (incl. country code)

2. Has your institution performed ANY minimally-invasive (laparoscopic or robot-assisted) pancreatoduodenectomies between 2012-2016?
   (Yes/No)

3. Please state who was responsible for the data collection in this study: (e.g. medical student supervised by a surgeon; dedicated resident; PhD candidate).
   (Multiple choice)

4. Please state who was responsible for the data collection in this study? (e.g. medical student supervised by a surgeon; PhD candidate/research fellow; dedicated resident/clinical fellow; surgeon).
   (Drop down)
5. Please state how collection of preoperative, perioperative, and postoperative variables was performed:
   a. Prospectively maintained database;
   b. Retrospective medical record review of digital records;
   c. Retrospective medical record review of paper records;
   d. Other

SURGICAL EXPERTISE QUESTIONS

6. When was the first PANCREATODUODENECTOMY (MIPD) performed at your institution?
   (Date)

7. How many MIPDs has your center performed in total?
   (Number: 0-99)

8. Please provide the actual number of pancreatoduodenectomy (all indications) at your institution for each year 2012 - 2016?
   (Number: 0-99)

9. What is typically the composition of the team that performs MIPD (e.g. 2 surgeons, 1 fellow or 1 surgeon, 2 residents)
   (Multiple choice)

10. In any given year, on average, how many different surgeons perform MIPD at your institution?
    (Number: 0-99)

11. Please describe the general criteria used by your institution to select patients for either MIPD or OPD.
    (Free text)

12. Do you perform MIPD with vascular resection?
    (Yes/ No)
### Appendix 3

**STROBE Checklist on the reporting of observational studies.**

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
</tr>
<tr>
<td></td>
<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>2</td>
</tr>
<tr>
<td>Background/rationale</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>3</td>
</tr>
<tr>
<td>State specific objectives, including any prespecified hypotheses</td>
<td></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>4</td>
</tr>
<tr>
<td>Study design</td>
<td>Present key elements of study design early in the paper</td>
</tr>
<tr>
<td>Setting</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
</tr>
<tr>
<td>Participants</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</td>
</tr>
<tr>
<td></td>
<td>(b) For matched studies, give matching criteria and number of exposed and unexposed</td>
</tr>
<tr>
<td>Variables</td>
<td>7</td>
</tr>
<tr>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
<td></td>
</tr>
<tr>
<td><strong>Data sources/measurement</strong></td>
<td>8*</td>
</tr>
<tr>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
<td></td>
</tr>
<tr>
<td><strong>Bias</strong></td>
<td>9</td>
</tr>
<tr>
<td>Describe any efforts to address potential sources of bias</td>
<td></td>
</tr>
<tr>
<td><strong>Study size</strong></td>
<td>10</td>
</tr>
<tr>
<td>Explain how the study size was arrived at</td>
<td></td>
</tr>
<tr>
<td><strong>Quantitative variables</strong></td>
<td>11</td>
</tr>
<tr>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
<td></td>
</tr>
<tr>
<td><strong>Statistical methods</strong></td>
<td>12</td>
</tr>
<tr>
<td>(a) Describe all statistical methods, including those used to control for confounding</td>
<td></td>
</tr>
<tr>
<td>(b) Describe any methods used to examine subgroups and interactions</td>
<td></td>
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<tr>
<td>(c) Explain how missing data were addressed</td>
<td></td>
</tr>
<tr>
<td>(d) If applicable, explain how loss to follow-up was addressed</td>
<td></td>
</tr>
<tr>
<td>(e) Describe any sensitivity analyses</td>
<td></td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>13*</td>
</tr>
<tr>
<td>Participants</td>
<td>Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</td>
</tr>
<tr>
<td></td>
<td>(b) Give reasons for non-participation at each stage</td>
</tr>
<tr>
<td></td>
<td>(c) Consider use of a flow diagram</td>
</tr>
<tr>
<td>Descriptive data</td>
<td>14*</td>
</tr>
<tr>
<td>(a) Give characteristics of study participants (eg demographic, clinical, social)</td>
<td></td>
</tr>
</tbody>
</table>
and information on exposures and potential confounders

(b) Indicate number of participants with missing data for each variable of interest

(c) Summarise follow-up time (eg, average and total amount)

<table>
<thead>
<tr>
<th>Outcome data</th>
<th>15*</th>
<th>Report numbers of outcome events or summary measures over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main results</td>
<td>16</td>
<td>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Report category boundaries when continuous variables were categorized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</td>
</tr>
<tr>
<td>Other analyses</td>
<td>17</td>
<td>Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses</td>
</tr>
</tbody>
</table>

**Discussion**

| Key results | 18 | Summarise key results with reference to study objectives |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |

**Other information**

| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for exposed and unexposed groups.