

BMJ Open Protocol of a prospective study investigating the association of PANcreatic parenchymal RISk factors with postoperative pancreatic fistula after partial pancreaticoduodenectomy (PARIS trial)

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ABSTRACT

Introduction Partial pancreatoduodenectomy (PD) is the treatment of choice for many malignant and benign diseases of the pancreatic head. Postoperative complication rates of up to 40% are regularly reported. One of the most common and potentially life-threatening complication is the postoperative pancreatic fistula (POPF). Parenchymal risk factors like main pancreatic duct diameter or texture of the pancreatic gland have already been identified in retrospective studies. The aim of this study is to evaluate the diagnostic value of parenchymal risk factors on POPF in a prospective manner.

Methods and analysis All patients scheduled for elective PD at the Department of General, Visceral and Transplantation Surgery of the University of Heidelberg will be screened for eligibility. As diagnostic factors, diameter and texture of the pancreatic gland as well as radiological and histopathological features will be recorded.

Furthermore, the new four class risk classification system by the International Study Group of Pancreatic Surgery (ISGPS) will be recorded. The postoperative course will be monitored prospectively. The primary endpoint will be the association of the main pancreatic duct size and the texture of the pancreatic gland on POPF according to the updated ISGPS definition. The diagnostic value of the above-mentioned factors for POPF will be evaluated in a univariable and multivariable analysis.

Ethics and dissemination PARIS is a monocentric, prospective, diagnostic study to evaluate the association of parenchymal risk factors and the development of POPF approved by the Ethics Committee of the medical faculty of Heidelberg University (S-344/2019). Results will be available in 2022 and will be published at national and international meetings. With this knowledge, the intraoperative and perioperative decision-making process could be eased and improve the individual outcome of patient.

Trial registration number DRKS00017184.

Strengths and limitations of this study

- A strength of this study is its prospective design and the application of valid applicable definitions for the main endpoints.
- In this trial the texture of the pancreatic gland is measured with all known methods including haptic, radiological and pathological measurement as well as the usage of a durometer.
- The trial is based on the results of a recently published systematic review investigating the association of pancreatic parenchymal risk factors with postoperative pancreatic fistula.
- This trial is the first study investigating and validating the recently established International Study Group of Pancreatic Surgery pancreatic parenchymal and main pancreatic duct size classification in a prospective design.
- A limitation of this trial is the monocentric design at the university hospital Heidelberg with the well-known issue of a compromised external validation.

INTRODUCTION AND SCIENTIFIC BACKGROUND

Partial pancreatoduodenectomy (PD) is the treatment of choice for numerous malignant and benign disease of the pancreas. Although postoperative mortality after PD has decreased below 5%,¹ morbidity remains high even in designated pancreatic cancer centres. Postoperative complication rates of up to 40% are regularly reported in prospective studies.^{2–4} Postoperative complications have been uniformly defined by the International Study Group for Pancreatic Surgery (ISGPS) over the last decades and allows standardised reporting of postoperative pancreatic fistula (POPF).⁵

POPF is one of the most frequent PD-associated complications occurring in 15%–30% of the patients^{2 3 6} with a POPF related haemorrhage as possible result which represents the most severe complication after PD.^{1 5} Multiple risk factors have been identified that are associated with the development of POPF following PD including patient-associated risk factors like body mass index (BMI),⁷ perioperative risk factors and surgeon-associated risk factors (experience in PD surgery). Furthermore, a number of pancreas-associated risk factors have been proposed in the literature including histology,⁸ a small diameter of the main pancreatic duct (MPD),^{7 9 10} soft pancreatic texture^{3 11} and an excentric location of the pancreatic duct.¹² However, a prospective study assessing the diagnostic value of different parenchymal characteristics is lacking.

Pancreas-associated risk factors are clinically important as they would offer the opportunity for an easy-to-use risk classification, that might guide intraoperative and post-operative decision-making process including placement of drains, degree of resection, intensity of follow-up, need for intensive care observation, administration of somatostatin analogues and others.

Aim of the study

PARIS trial is a monocentric, prospective, diagnostic study with one study arm. The aim of this study is to evaluate the impact of MPD size and pancreatic texture as pancreas specific risk factors for the development of clinically relevant POPF. Furthermore, it aims to evaluate and validate a new four grouped parenchymal classification system including the combination of the diameter of the MPD (≤ 3 mm vs > 3 mm) and the texture of the pancreatic gland (soft, hard), in order to calculate intraoperatively the probability of a POPF during the clinical course.

METHODS

The PARIS trial is a monocentric, prospective, diagnostic study with the aim to investigate the impact of the MPD size and the parenchymal texture on the risk of a development of a POPF. According to the aim of this trial and the primary and secondary endpoints the following methodical tools were used.

Study population

Adult patients scheduled for elective PD for any indication at the department of general, visceral and transplantation surgery at the University Hospital of Heidelberg will be screened for eligibility and will be asked to participate. According to the aim of this trial all patients with the necessity of changing the surgical intervention to a total/distal pancreatectomy or no partial pancreatectomy for any reason, will be excluded for further investigations and observations.

The inclusion and exclusion criteria are illustrated in [table 1](#).

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Scheduled for elective partial pancreaticoduodenectomy ▶ Ability of subject to understand character and individual consequences of the clinical trial ▶ Age ≥ 18 years ▶ Written informed consent 	<ul style="list-style-type: none"> ▶ Participation in an interventional trial with interference of intervention and outcome of this study ▶ Patients with a legal guardian ▶ Language problems

Diagnostic factors

The following diagnostic analyses will be performed in the study:

1. Preoperatively a radiologist will evaluate the density of the pancreatic parenchyma and the diameter of the MPD at the future pancreatic resection line (ventral of the superior mesenteric vein (SMV)) via CT scan using the portal venous phase as imaging set. In case of a MPD too small to be measured radiologically, the duct diameter will be rated as 1 mm.
2. A detailed histopathological investigation by an experienced pathologist will follow the surgical intervention in order to record the grade of fibrosis, lipomatous atrophy, inflammatory infiltration, inflammatory activity and microscopic necrosis at the pancreatic resection margin according to the Heidelberg grading system ([table 2](#)).¹³ The pathological work-up will be performed as published and described previously.¹³
3. The pancreatic texture will be measured at the pancreatic resection margin using a shore durometer (Schmidt Control Instruments, PHPSO, Hans Schmidt and Co, Waldkreiburg, Germany) in order to get an objective recorded value of the pancreatic texture and its density measured in Shore units. The measurement will be performed as described by Belyaev *et al.*¹⁴ Briefly, stiffness of the gland will be measured in the resected specimen at the transection line using the durometer. The mean value of three measurements at different positions on the transection line will be recorded.
4. The pancreatic texture will be evaluated by an experienced senior surgeon and classified as ‘soft’, ‘hard’, ‘cannot decide’.
5. The width of the MPD will be measured and recorded as well as documented with an intraoperative photograph. The classification of the diameter will be recorded as continuous variable in mm after probing the MPD once.
6. Intraoperatively, there will be a classification of the pancreatic gland according to a newly proposed four grouped ISGPS pancreatic duct and texture classification system.¹⁵ An illustration of the described classification system can be seen below ([table 3](#)).

Trial site and sample size

The trial will be performed at the Department of General, Visceral and Transplantation Surgery of the

Table 2 Histological grading according to Felix *et al*¹³

Grading	Fibrosis	Lipomatous atrophy	Inflammatory infiltrations	Inflammatory activity	Microscopic necrosis
0	No	No	No	No	No
1	Periductal	Little	Little	Little	Single cells
2	Periductal, intralobular and interlobular	Moderate	Moderate	Moderate	Grouped necrosis
3	Extensive	Severe	Severe	Severe	Broad

University Hospital Heidelberg. Patients will be continuously recruited until the planned trial population of 200 patients to be analysed is reached. Based on the department's data and the expected number of partial pancreaticoduodenectomies per year, the recruitment will end approximately 18 months after the first included patient, starting in January 2020. We planned a total duration of the trial of 22 months beginning with the first included patient to the final analysis of the results.

Outcomes

Due to the nature of a diagnostic trial the association of the following endpoints with the diagnostic criteria described above will be investigated.

Primary endpoint

The primary endpoint of the study is the association of the above mentioned diagnostic factors and POPF, defined as type B and C POPF according to the ISGPS updated version of 2016⁵ within 30 days after index surgery. In order to investigate the diagnostic value of predicting a clinically relevant POPF (CR-POPF) using specific characteristics of the pancreatic gland, the positive and negative predictive value, sensitivity and specificity will be calculated. The association will be expressed by OR with corresponding 95% CI and descriptive p values.

Secondary endpoints

The same associations will be calculated for the following secondary endpoints within 30 days after index surgery:

1. Delayed gastric emptying as defined by the ISGPS¹⁶ at visits 3, 4 and 5.
2. Postpancreatectomy haemorrhage as defined by the ISGPS¹⁷ at visits 3, 4 and 5.
3. Chyle leakage as defined by the ISGPS¹⁸ at visits 3, 4 and 5.

Table 3 Pancreatic texture and duct classification

Grade	Texture	Diameter of the MPD
A	Not-soft/hard	>3 mm
B	Not-soft/hard	≤3 mm
C	soft	>3 mm
D	soft	≤3 mm

MPD, main pancreatic duct.

4. Bile leakage as defined by the International Study Group of Liver Surgery (ISGLS)¹⁹ at visits 3, 4 and 5.
5. Postoperative morbidity and mortality of the above mentioned pancreas specific or any other complications according to the Clavien-Dindo Classification^{20 21} at visits 3, 4 and 5.
6. Postoperative length of hospital stay (in days from index operation) at visits 4 and 5.

In addition to the above-mentioned endpoints, the following confounders will be documented:

1. Experience of surgeon (number of previously performed Whipple procedures).
2. BMI of the patient.
3. Indication for surgery (chronic pancreatitis, ductal adenocarcinoma, Intraductal Papillary Mucinous Neoplasm (IPMN), neuroendocrine tumour, distal bile duct cancer, other).
4. Age (in years) of the patient
5. American Society of Anesthesiologists classification.
6. Type of surgical access (open vs minimal invasive/robotic).
7. Use of somatostatin analogues.
8. Prior neoadjuvant (radio)chemotherapy.
9. Preoperative total bilirubin.
10. Volume and type of intraoperative intravenous fluids.
11. Current medication (glucocorticoids, immunosuppressive drugs, somatostatin analogues).
12. Preoperative biliary drainage, inclusively type of the placement of the drain (endoscopic, percutaneous or operative).
13. Comorbidity according to the updated Charlson Comorbidity Index.²²
14. Intraoperative blood loss.
15. Necessity of an arterial resection (eg, coeliac trunk, hepatic artery, superior mesenteric artery (SMA), splenic artery).
16. Necessity of a venous resection (eg, portal vein, superior mesenteric vein (SMV), splenic vein).
17. Location of the pancreatic duct (ventral, centre, dorsal).
18. Degree of stomach resection (pylorus preserving, pylorus resecting, classical PD, (sub)total gastrectomy).
19. Performance of a resection of other organs which are not part of the PD (eg, right/left hemicolon, transverse colon, spleen, segment bowel resection, partial liver resection).

Study conduct and trial visits

Visit 1

All consecutive patients are screened for potential inclusion. Eligible patients are asked for informed consent. For enrolled patients the following data items will be collected: (1) demographic data; (2) baseline data and (3) medical history/comorbidities.

Visit 2

Visit 2 will take place in the operation theatre by an experienced senior surgeon giving detailed information about the anatomic situation before and after the surgical resection as well as the extend of resection. In addition, the following data items are collected:

1. Date of surgery.
2. Typ of the surgical access (open vs laparoscopic/robotic).
3. Duration of surgery (in min, start of skin incision to end of skin closure).
4. Duration of pancreatojejunostomy (in min).
5. Estimated blood loss from the anaesthesiology report (in mL).
6. Degree of pancreatic resection, stomach resection, vascular resection with detailed description of the performed reconstruction procedures.
7. Performed triangle operation (dissection of all tissue between SMA, coeliac trunk and portal vein/SMV).
8. Resection of other organs (eg, right/left hemicolon, transverse colon, partial liver resection, segment of small bowel, spleen).
9. Texture of the pancreatic gland (soft vs hard/not-soft).
10. Diameter and localisation of the MPD.
11. Insertion of abdominal drains.
12. Experience of the surgeon performing the anastomosis (≤ 50 Whipple procedures vs > 50 Whipple procedures).

Visits 3 and 4

After the operation, the postoperative course will be observed prospectively. Visits 3 and 4 are identical, however, visit 3 will be performed on postoperative day (POD) 3–7, while visit 4 is performed on POD 10–14 or at discharge, whatever comes first.

During these visits, the postoperative complications (primary and secondary endpoints) as mentioned above will be recorded and documented in the electronic case report form (eCRF). All above-mentioned complications will also be classified according to the classification system of Clavien-Dindo.^{20 21}

Visit 5

Visit 5 will occur on POD 30. It can be performed in person if the patient is still in hospital or returns for an outpatient visit, or via the phone. The data collection includes the identical information extracted for visits 3 and 4. Additionally, histopathological assessment will be recorded.

A detailed illustration of the study conduct and the included visits can be seen in [table 4](#).

Data management

An eCRF implemented in the REDCap system^{23 24} will be used for data collection. To assure a safe and secure environment for the acquired data, the system used for remote data entry is validated and is compliant with Food and Drug Administration (FDA) 21 CFR part 11. Data transmission will be encrypted with secure socket layer technology. The database server will be located in a secure data centre and be protected by a firewall. Only authorised users will be able to enter or edit data. All changes to data will be logged with a computerised timestamp in an audit trail. All clinical data will be pseudonymised. Backups will be conducted regularly.

Table 4 Study visits and data items

Activity	Visit 1 (Screening, enrolment)	Visit 2 (surgery)	Visit 3 and 4 (POD 3–7 and 10–14 or at discharge) (respective visits are omitted if patient has been discharged before)	Visit 5 (POD 30)
Informed consent	X			
Eligibility criteria	X			
Demographics and baseline clinical data	X			
Density measurement from CT or MRI	X			
Surgical data		X		
Durometry		X		
Intraop. Photo documentation with ruler		X		
Assessment of primary endpoint			X	X
Assessment of secondary endpoints			X	X
Histopathology				X

POD, postoperative day.

All data collected will be integrated in a statistical analysis system. After database closure access rights will be granted to the responsible biometrician for statistically analysis.

Statistical analysis

To investigate the primary objective of this trial, the patients will be divided into several groups according to the recorded parenchymal characteristics. Therefore, they will be dichotomised in soft and hard pancreatic texture as well as in $>3\text{mm}$ and $\leq 3\text{mm}$ diameter of the MPD. If the pancreatic texture was classified as 'cannot decide' intraoperatively, the patients will be excluded for the primary analysis. For sensitivity analyses this group of patients will be added to the soft as well as to the hard texture group.

Furthermore, the included patients will be divided according to the allocated group of the pancreatic duct and texture classification (ie, Group A–D).

In the next step, the postoperative complications according to Clavien-Dindo, ISGPS and ISGLS will be analysed and the patients will be dichotomised whether they had a clinical relevant POPF (yes/no). If they had a POPF a more detailed differentiation will be done (grade B or Grade C).⁵

To evaluate the primary endpoint each pancreatic parenchyma characteristic (predictor) will be evaluated for its association with POPF. Therefore, in a first step, univariate analysis will be performed. For dichotomous, nominal and ordinal variables contingency table will be created and will be analysed by chi-square tests. For continuous variables, t-tests will be performed. Furthermore, to analyse the prediction performance of each of the possible predictors and confounders, for dichotomous variables sensitivity, specificity, positive and negative predictive values will be calculated. For ordinal and continuous variables univariate logistic regression models will be used and the respective area under the curve (AUC=c-index) will be calculated. Additionally, association with POPF will be described by ORs with corresponding 95% CI and descriptive p values. In the same way, each of the potential confounder, as listed under 'confounders' above, will be also evaluated regarding to their association with POPF.

In order to find the most important influence factors on POPF, multivariable logistic regression analysis will be performed by best subset selection and forward selection (based on the Akaike information criterion). Thereby, missing values will be imputed by multiple imputation. Variables comprised by the final model will be found in the set of predictors and confounders analysed in the univariate analyses. Assuming a prevalence of about 20% the final model will comprise up to four different predictors or confounders. The results will be summarised by AUCs, ORs with corresponding 95% CI and descriptive p values. Based on the sample size of $n=200$, the resulting widths of the confidence intervals calculated in the models are 13.1% (based on an AUC value of 0.8).

If there will be enough patients having a POPF grade C⁵ as postoperative complication, a subgroup analysis discriminating CR-POPF grade B and C⁵ will be performed.

Secondary endpoints will be analysed descriptively by tabulation of the measures of the empirical distributions. According to the scale level of the variables, means, standard deviations, medians, first and third quartiles, minimum and maximum or absolute and relative frequencies will be reported, respectively. P values of further statistical tests and corresponding 95% confidence intervals will be given.

Since this study is of an observational character all p values will be interpreted in a descriptive manner without confirmatory value and p values smaller than 0.05 are determined as significant in a descriptive sense.

Statistical analysis will be performed based on the statistic software R version $>4.0.0$.²⁵

Quality assurance

Monitoring

Monitoring will be done to ensure compliance with the trial protocol, the principles of the Declaration of Helsinki and ICH Good Clinical Practice as well as data protection and other relevant legal aspects. Only a centralised digital monitoring via the eCRF will be conducted using plausibility checks.

Assessment of safety

The primary and secondary endpoints include all necessary safety endpoints. No additional safety analysis will be performed in the PARIS study. For clinical trials according to Medical Association's professional code (Berufssordnung der Bundesärztekammer) §15 no specific SAE management is required.

Methods for minimising bias

Minimising selection bias

All patients will be consecutively screened and if found to be eligible, informed consent will be obtained. The amount of screened, included and analysed patients will be reported as well as the number of patients who were subsequently excluded or the participation of the trial was determined. For all differences there will be detailed explanations.

Minimising performance and detection bias

Data capturing on pancreatic parenchyma characteristics and outcome assessment will be performed by two different investigators. Postoperative clinical investigators of the clinical course will be blinded to the intraoperative results, as well as the investigating radiologists and pathologist. Statistical analysis will be performed by a biometrician after closure of database.

Minimising attrition bias

Statistical measurements such as imputation will be taken to minimise risk of bias due to incomplete outcome data.²⁶ The trial will be reported according to the updated



Standards for Reporting of Diagnostic Accuracy statement.²⁷ The trial is registered with Deutsches Register Klinischer Studien. To avoid the risk of selective reporting, the trial protocol with full information about endpoints and profound explanation of planned statistical analysis is hereby published according to the Standard Protocol Items: Recommendations for Interventional Trials statement where appropriate.²⁸

Minimising other bias

Any financial relationship or any conflict of interest that could influence the work within this project will be named specifically. Confounding will be minimised by the inclusion of covariates and factors in the statistical analysis of the primary endpoint as mentioned in the statistical analysis section described previously.

Ethics and dissemination

The present trial will be conducted in accordance with the 'Ethical principles for medical research involving human subjects' of the 18th World Medical Association General Assembly in Helsinki (1964), the Declaration of Helsinki in its actual version,²⁹ the internationally recognised Good Clinical Practice Guidelines, German state and national laws and regulations for data protection and the German Medical Association's Code of Conduct.

As recommended in the professional code for physicians in Germany (§15 BOÄ) the protocol of this trial has been reviewed and approved by the Ethics Committee of the medical faculty of the University of Heidelberg before the trial started or this paper was published (S-344/2019). Any amendments will be re-evaluated and approved by the responsible independent ethics committees.

Before any patient is included in this trial a detailed conversation between a surgeon and the patient will take place in which all information (e.g., aims, conflicts, conduct, duration, possibility of termination of the participation without naming any reasons, possibility of the deletion of all gathered data in case of a termination of the participation, methods, possible benefits and risks) will be discussed. These information will be shared in oral as well as in written form.

The patients free will to be part of the trial will be documented by signature on the informed consent form. All patient related data is subject to medical confidentiality to the Federal Data Protection Act. All data transfers will be done by using pseudonyms. Third parties will not have any insight in original data.

DISCUSSION

The PARIS trial is a monocentric, prospective, diagnostic trial with one arm and the aim to investigate the diagnostic value of different parenchymal characteristics of the pancreatic gland including the pancreatic texture, the diameter of the MPD and their combination as prediction

factors of a CR-POPF. These results should help to validate a newly developed simple four-stage classification system (table 3). This classification system in turn, aims to help reporting and intraoperative decision making, especially concerning the extent of the resection procedure, the way of reconstruction, the necessity of abdominal drains and the need of observation on an intensive care unit or further medication.

The results will also be used to evaluate the new classification system of preoperatively/and intraoperatively measured parenchymal characteristics in order to estimate the risk of a CR-POPF during the clinical course. This new classification system has four groups including the most important parenchymal risk factors (texture and diameter of the MPD) in combination. The classification system is based on the results of a systematic review.¹⁵ The results of this systematic review showed a significant association of a soft pancreatic gland and a small MPD with the development of a clinically relevant POPF. In sum, the classification system is based on retrospective data sets but needs more trials, especially in a prospective design to be evaluated.

Another strength of this prospective trial, next to its design, will be the objective evaluation of the pancreatic texture. Not only the haptic evaluation of a senior surgeon will be used, but there will be radiological and histopathological diagnostics, too. These methods, and the usage of a durometer to get objective results of the density of the pancreatic texture, compared with the assessment of the senior surgeon, allow representative results for the parenchymal characteristics and therefore, valid investigations of the association of parenchymal risk factors with clinically relevant POPF.

As limitation of this trial can be seen that it will be performed as a single centre study at the University Hospital Heidelberg, which is high-volume pancreatic centre. Therefore, external validity might be compromised and the results might not be representative. However, because of the large volume and the broad and heterogeneous population at our centre, generalisability of results is ensured.

According to the aim of this trial the main focus is placed on the association of pancreatic gland characteristics on the risk of developing a clinically relevant POPF, which results in another limitation of this trial, as other risk factors described in several fistula risk scores are not equally analysed. Nevertheless, parameters of the alternative fistula risk score⁷ or the original fistula risk score³⁰ are included as confounders in this trial. Therefore, the impact of these risk factors can be investigated and they will be included in multivariate analyses.

Another limitation of this trial is that due to a lack of clear data regarding the impact of the investigated risk factors and, especially the combination of those factors, an adequate diagnostic sample size calculation was not possible at this time, as there is no data on the new ISGPS classification yet. Therefore, more studies investigating the issue of this trial will be needed.

In sum, the design of this trial and the included population make it possible to work off the existing relevant lack of studies investigating the association of parenchymal risk factors and the development of a POPF in a prospective study design.

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