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# Gastric venous reconstruction to reduce gastric venous congestion after total pancreatectomy: study protocol of a single-centre prospective non-randomised observational study (IDEAL Phase 2A) - GENDER study (Gastric vENous DrainagE Reconstruction)

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## ABSTRACT

**Introduction** Total pancreatoduodenectomy (TP) is the standard surgical approach for treating extended pancreas tumours. If TP is performed with splenectomy, the left gastric vein (LGV) sometimes needs to be sacrificed for oncological or technical reasons, which can result in gastric venous congestion (GVC). GVC can lead to gastric venous infarction, which in turn causes gastric perforation with abdominal sepsis. To avoid gastric venous infarction, partial or total gastrectomy is usually performed if GVC occurs after TP. However, gastrectomy can be avoided by reconstructing the gastric venous outflow to overcome GVC and avoid gastric venous infarction. The current study aims to assess the role of gastric venous outflow reconstruction to prevent GVC after TP and avoid gastrectomy.

**Methods and analysis** In the current single-centre observational pilot study, 20 patients will be assigned to study after intraoperative evaluation of gastric venous drainage after LGV resection during TP. During surgery, on-site evaluation by the surgeon, endoscopic examination, indocyanine green, gastric venous drainage flowmetry and spectral analysis will be performed. Postoperatively, patients will receive standard post-TP care and treatment. During hospitalisation, endoscopic examination with indocyanine green will be performed on the 1st, 3rd and 7th postoperative day to evaluate gastric ischaemia. Ischaemia markers will be evaluated daily after surgery. After discharge, patients will be followed-up for 90 days, during which mortality and morbidities will be recorded. The main endpoints of the study will include, rate of GVC, rate of gastric ischaemia, rate of postpancreatectomy gastrectomy, rate of reoperation, morbidity and mortality.

**Ethics and dissemination** The study protocol has been reviewed and approved by the Ethics Committee of the University of Heidelberg. The results will be actively disseminated through peer-reviewed journals and conference presentations, and are expected in 2022.

**Trial registration number** NCT04850430.

## Strengths and limitations of this study

- This is the first prospective study, which evaluates the effect of the gastric venous reconstruction on gastric venous congestions and surgical outcomes of the patients undergoing total pancreatectomy with splenectomy and additional left gastric vein resection.
- The complex intervention of gastric venous reconstruction will be carried out in a large scale of patients for the first time, whereas current reports in the literature include only case reports.
- This observational study will be carried out without randomisation or control group.
- Generalisability of the outcomes might be restricted to highly qualified facilities and tertiary referral hospitals with high volume of pancreas surgeries.

## INTRODUCTION

Total pancreatoduodenectomy (TP) is the standard surgical approach for treating extended pancreas tumours. Patients undergoing TP to treat malignant lesions often undergo splenectomy at the same time for oncological reasons,[1 2] which can disrupt venous drainage of the stomach. The stomach is drained via three major routes: (1) the distal stomach is drained via the right gastric and the right gastroepiploic vein, (2) the greater curvature is drained via the short gastric veins and the left gastroepiploic vein into the splenic vein and (3) the lesser curvature is drained via the left gastric vein (LGV).[3 4] When TP is performed together with splenectomy, the LGV sometimes has

to be sacrificed for oncological or iatrogenic technical reasons. This causes gastric venous congestion (GVC) because the major venous draining routes are terminated. GVC leads to gastric venous infarction and eventually to ischaemia with subsequent gastric perforation and abdominal sepsis, thereby increasing morbidity and mortality after TP. To avoid gastric venous infarction, partial or total gastrectomy is frequently performed if GVC occurs.[3 4]

Reconstructing the gastric venous outflow may reduce the risk of gastric venous infarction or ischaemia and avoid the need for gastrectomy, which significantly increases postoperative morbidity and mortality as well as impairing the patient's quality of life.[5] There are several possible approaches to reconstructing the gastric venous outflow, including (a) anastomosis of the LGV to the portal or renal vein, (b) anastomosis of the right gastroepiploic vein to the portal, middle colic or left renal vein and (c) anastomosis of the right gastric vein to the portal vein. However, the role of gastric venous outflow reconstruction has not been comprehensively evaluated in the literature, and only few case reports have reported a reduction in the rates of gastrectomy, reoperation and complications.[1–5]

Developing techniques to reconstruct gastric venous outflow to decrease GVC in patients undergoing TP may lead to advances in surgical treatment. Following phase 2a of the IDEAL criteria,[6] we will prospectively include 20 patients scheduled to receive TP with splenectomy and necessary ligation of the LGV, who do not have an oncological indication for gastrectomy.

## METHODS

### Study design

This is a single-centre, prospective, single-arm, observational study. The university ethics committee has approved the study protocol (registry number: S-173/2021) and the study has been registered at ClinicalTrials.gov. Any amendments to the trial protocol will be submitted for review to the institutional review board. Trial registrations will be updated, and participants will be informed about the risks and benefits of participation both verbally by one of the investigators and in writing in the form of a patient information brochure. Participants will only be included after written informed consent has been obtained. Patients can withdraw their participation at any time for any reason and without any consequences. The investigator can also withdraw a patient from the study for urgent medical reasons. Patient data will be anonymised and stored in a secure database.

### Population

The current study aims to assess 20 patients, in line with the IDEAL 2a recommendation to include a low number of patients.[6 7] All evaluations and analyses will take place at the Department of General, Visceral and Transplantation Surgery of the University of Heidelberg. This study will be initiated in 2021 and is expected to last until 2022. All patients meeting the inclusion criteria will be informed about the study protocol, potential benefits and side effects of the procedures (tables 1 and 2).

Eligible patients will receive a written informed consent statement. Patients that agree to participate and sign the informed consent form will be recruited and baseline demographic and clinical characteristics will be recorded (figure 1). The patients will be assigned to study after intraoperative evaluation of gastric venous drainage after LGV resection during TP.

### Intervention

Preoperatively, the LGV will be assessed and characterised using CT angiography. However, LGV might not be always representable, particularly in patients with congested splenic vein due to local obstacles or stenosis. Patients undergoing TP with splenectomy and ligation of the LGV and who do not have an oncological indication for gastrectomy will be included. The gastric venous outflow will be reconstructed after TP using the technique described by Hackert *et al*.[8] The patients will be assessed concerning GVC and gastric ischaemia intraoperatively before and after venous outflow reconstruction through on-site evaluation by the surgeon, endoscopic examination, indocyanine green (ICG), gastric venous drainage flowmetry and spectral imaging. After surgery, patients will receive standard post-TP care and treatment. During hospitalisation, endoscopic examination with ICG will be performed on the 1st, 3rd and 7th postoperative day to evaluate gastric ischaemia (table 3). Ischaemia markers will be evaluated daily after surgery. After discharge, patients will be followed up for 90 days, during which mortality and morbidity will be recorded.

### Outcome measures

#### Primary endpoints

In this study, the rate of postoperative partial, subtotal or total gastrectomy after gastric venous outflow reconstruction, will be assessed. If GVC occurs after TP, the gastric venous drainage will be reconstructed. Any subsequent failure in venous drainage followed by GVC and ischaemia will be managed by gastrectomy (total or partial) as necessary.

The following primary endpoints will also be assessed: intraoperative and postoperative GVC and gastric ischaemia, gastric venous outflow, intraoperative gastric venous drainage, reoperation rate, morbidity rate and mortality rate (table 4).

### Patient and public involvement

The patients and public were not involved in the planning of this study.

### Modification of the protocol

Protocol amendments will be considered by the principal investigator. All protocol amendments will be submitted to the ethics committee for approval.

**Table 1** The study design according to the Standard Protocol Items: Recommendations for Interventional Trials checklist

| Visit | Day−1 Admission and screening | OP day | 30 min before procedure | 60 min after procedure | POD 1 | POD 3 | POD 7 | POD 14 | POD 30 | POD 90 |
|---|---|---|---|---|---|---|---|---|---|---|
| Baseline data | x | | | | | | | | | |
| Eligibility criteria | x | X | | | | | | | | |
| Surgical procedure | | X | | | | | | | | |
| Endpoint assessment | | X | x | x | x | x | x | x | x | x |
| Safety assessment | x | X | | | x | x | x | x | x | x |

OP, operation; POD, postoperative day.

## Study termination

To minimise biases, mortalities, adverse events and complications will be documented on separate forms and this information will be used to analyse safety. The principal investigator may terminate the study at any time in consultation with the key research associates and the biostatistician. Possible reasons for the termination include a high mortality rate or complications that present a potential health hazard. In addition, external evidence may indicate that premature termination is required. Patients will be immediately taken out of the study if informed consent is withdrawn. The patients will not have to explain their withdrawal, and withdrawal will not affect their future medical care. The investigator may also exclude patients for other reasons, such as adverse effects on the patient's well-being. Patient withdrawal will be documented in the case report form. Any financial relationship and any conflict of interest that may arise will also be declared.

## Data management

The participant will receive post-TP care and treatment that is routine at our institution. Complications will be described according to the Clavien-Dindo classification and International Study Group of Pancreatic Surgery standards and will be observed to assess the safety of surgical procedures. Only intervention-related events that occur during surgery and follow-up will be collected. All intervention-related complications will be documented and reported. Complications will be assessed and documented until the end of follow-up. Results will be evaluated in the clinical report. Complications or adverse events will be collected from patients' documents and will be assessed by the investigator. At each visit, the investigator will ask the patient if they have experienced complications since the last visit. The attending physician must report major complications to the principal investigator within 24 hours. The initial report must be as complete as possible, including details of the current illness, adverse events and an assessment of the causal relationship between the event and the study treatment. The investigator must ensure that adequate medical care is provided during and following participation in the study. Patients will receive adequate treatment in every clinical situation, including emergencies. In addition, the patient outcomes will be closely monitored.

## Statistical design and analysis

### Sample size

This is an exploratory pilot study, so a formal sample size calculation will not be made. Twenty patients will be evaluated in this study.

## Statistical analysis

Statistical analysis will be performed based on the intention-to-treat populations using SPSS software Version 27.0. The incidence of categorical outcomes (GVC and gastric ischaemia) will be presented as proportions. Continuous data will be presented as mean and SD. Finally, a descriptive p value will be calculated.

Table 2 Inclusion and exclusion criteria of the study

| Inclusion criteria | Exclusion criteria |
|---|---|
| ► Age ≥18 years.<br>► Provide written informed consent.<br>► Elective total pancreatectomy for malignant or benign pancreatic lesions or chronic pancreatitis with splenectomy.<br>► Intraoperative ligation of left gastric vein necessary. | ► Gastric resection due to malignant infiltration.<br>► Non-reconstructable gastric venous drainage.<br>► Previous pancreas surgery. |

## Ethics and dissemination

This protocol study was approved by the independent Ethics Committee of the University of Heidelberg (registration number: S-173/2021). All study protocols will follow the 2013 Helsinki Declaration. Enrolment will be voluntary and consent may be withdrawn at any time, without giving reasons and without affecting future medical care. The investigators will not be compensated to carry out the study and there will be no external financial support for this trial. Likewise, study participants will not be financially reimbursed for participating. Since the entire study incorporates fully licenced and approved methods, no additional compensation for harmful outcomes will be provided. Patients will be informed verbally and in writing about the nature and scope of the planned study, particularly about the possible health benefits and risks, before the start of the study. Patients will then give their approval by signing an informed consent form (online supplemental file 1). If a participant withdraws from the study, their data will be destroyed unless they give permission for their data to be used. Patient names and other confidential information will be protected by medical confidentiality agreements and the Bundesdatenschutzgesetz. Patient data will only be transferred in pseudonymised form. The results of this study will be published in a peer-reviewed journal and will also be presented at medical meetings.

## DISCUSSION

Gastric venous drainage reconstruction may avoid the need for gastrectomy by preventing GVC after TP. Although the outcomes of venous drainage reconstruction after TP have not been evaluated, a few case reports

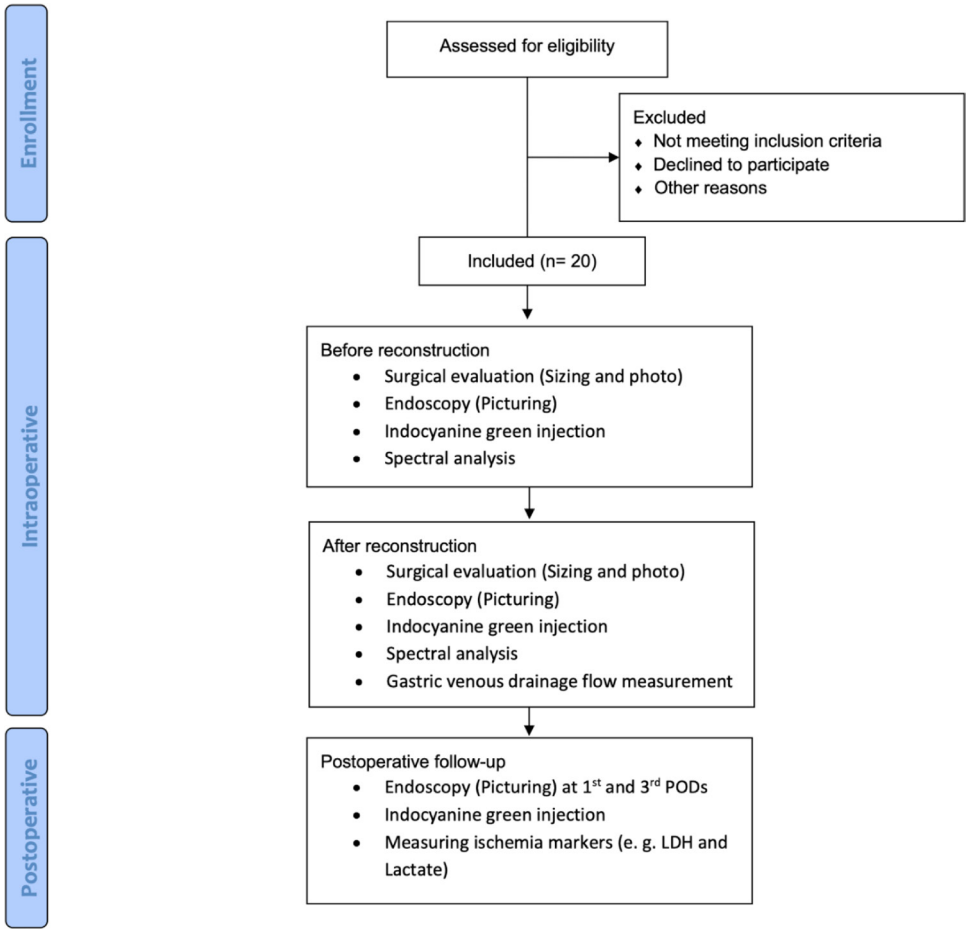


Figure 1 Study design flow chart. PODs, postoperative days.

Table 3 Timetable of the endpoint assessments during the study

| Visits | Items |
|---|---|
| Visit schedule and documentation | |
| Day 1 | On the first day, the following baseline data will be documented from eligible patients who have signed the informed consent form:<br>Demographic characteristics:<br>► Gender (female/male).<br>► Age (years).<br>► Height (cm).<br>► Weight (kg).<br>Baseline clinical data:<br>► Comorbidities (cardiac, pulmonary, renal, autoimmune and infectious).<br>► Medication. |
| Day of admission | ► Routine laboratory tests. |
| Operation day | ► Surgical procedure.<br>► Intraoperative outcome assessment before and after reconstruction procedure. |
| 1st, 3rd and 7th PODs | ► Assessment of main and secondary outcomes as described above.<br>► Assessment of complications according to Clavien-Dindo classification.<br>► Assessment of laboratory findings as described above. |
| 14th and 30th POD | |
| 14th and 30th POD | ► Assessment of main and secondary outcomes as described above.<br>► Assessment of complications according to the Clavien-Dindo classification.<br>► Calculation of the Comprehensive Complication Index. |
| 90th POD | ► Assessment of main and secondary outcomes as described above.<br>► Assessment of complications according to the Clavien-Dindo classification.<br>► Calculation of the Comprehensive Complication Index. |

POD, postoperative day.

have suggested that venous reconstruction is a safe approach with good early patency (table 5).

The LGV is physiologically important for gastric venous drainage, particularly during pancreatic surgery. If the splenic vein is disconnected from the portomesenteric venous axis during pancreatic resection, then the LGV is the main responsible route for gastric and splenic venous drainage.[8 9] Sacrificing the LGV without reconstruction in these cases can cause acute or chronic GVC, and subsequent complications such as delayed gastric emptying or gastric ischaemia.[8] Thus, preserving adequate drainage of the LGV during TP with splenectomy can not only decrease the perioperative morbidity but also redeem the stomach function and patient's quality of life.[8 10] The LGV also facilitates the drainage of the spleen and stomach and neutralises the risk of left-sided portal hypertension.[11 12]

Resection of all stomach drainage veins, including the LGV, may increase the risk of gastric congestion, ischaemia and the need for reoperation and gastrectomy. Reoperations and repeated resection after TP have a negative effect on the short-term and long-term outcomes. Therefore, reinserting the LGV may reduce complications, reoperations, hospitalisation time and mortality. The current study will be the first to evaluate the outcomes of gastric venous reconstruction following LGV resection in patients undergoing TP with splenectomy. The results of this study will provide a background for a prospective, multicentre IDEAL stage 2b study and will better define the indications for this technique.[13]

In summary, reconstruction of gastric venous drainage can prevent the serious complications of GVC after TP, so that gastrectomy can be avoided. Although various techniques have been introduced for reconstructing venous drainage of the stomach, reinserting the LGV is important for spleen and stomach drainage, particularly in patients who undergo TP with splenectomy. The current study will be the first to systematically and prospectively evaluate patient outcomes after TP with gastric venous reconstruction.

Table 4 Definition of the study endpoints

| Endpoints | Definitions |
|---|---|
| Intraoperative GVC | ► Intraoperative endoscopic evaluation of gastric mucosa regarding signs of congestion/ischaemia (before reconstruction and 30–60 min after venous drainage reconstruction). |
| Intraoperative evaluation of gastric ischaemia | ► Intraoperative injection of ICG for the real-time identification of gastric venous flow drainage (before reconstruction and 30–60 min after venous outflow reconstruction). |
| Spectral analysis of the gastric venous outflow | ► Intraoperative spectral analysis of the gastric perfusion at the beginning of surgery, before venous outflow reconstruction and 30–60 min after venous outflow reconstruction. |
| Intraoperative measurement of gastric venous drainage | ► Intraoperative measurement of gastric venous drainage flow after venous reconstruction (flowmetry). |
| Postoperative endoscopic assessment of GVC and/or gastric ischaemia | ► Postoperative endoscopic evaluation of congestion/ischaemia in the gastric mucosa (1st, 3rd and 7th PODs). |
| Postoperative assessment of GVC and/or gastric ischaemia (endoscopic plus fluorescent agent) | ► Postoperative evaluation of gastric ischaemia by endoscopic examinations with ICG (1st, 3rd and 7th PODs). |
| Postoperative assessment of gastric ischaemia (serum levels of ischaemia markers) | ► Daily postoperative measurement of serum levels of ischaemia markers, including lactate and lactate dehydrogenase. |
| Reoperation | ► Any reoperation to manage GVC, other than gastrectomy. |
| Postoperative morbidity<br>Mortality | ► Morbidity rates will be reported. Morbidities will be classified according to the Clavien-Dindo classification and ISGPS standards.<br>► The all-cause mortality rate will be reported until POD 90. |

GVC, gastric venous congestion; ICG, endoscopic examination with indocyanine green; ISGPS, International Study Group of Pancreatic Surgery; POD, postoperative day.

The GENDER study is expected to increase our understanding regarding the advantages and disadvantages of the gastric venous drainage reconstruction in order to prevent GVC and subsequent complications. In addition, the heterogeneity of the study group is considered to be minimal, since all patients will be operated due to malignant pancreas lesions with regional invasions. However, since this is the first study to evaluate the role of gastric venous drainage reconstruction, some limitations might not be avoidable. The lack of a control group who do not receive gastric venous reconstruction after sacrificing the LGV during total pancreatectomy should be considered as the main limitation of the study. Moreover, generalisability may be limited because the expertise to carry out

Table 5 Literature review of studies reporting gastric venous drainage reconstruction because of gastric venous congestion

| Study | Sample size | First procedure | Reconstruction technique |
|---|---|---|---|
| Sandroussi and McGilvray[14] | One patient | Radical TP with long-segment PV resection. | Anastomosis of LGV to IMV. |
| Barbier *et al*[1] | Three patients | Stomach-preserving TP. | Reconstruction of SV (n=1).<br>Reconstruction of LGV (n=1).<br>Reconstruction of LGV and RGV (n=1). |
| Hackert *et al*[8] | – | PP and TP. | Reinsertion of CV to PV. |
| Nakao *et al*[3] | One patient | Subtotal stomach-preserving TP with PV and SMV resection. | Anastomosis of RGEV and LOV. |
| Strobel *et al*[15] | One patient | EP with resection of the PV confluence. | Distal spleno-renal shunt (anastomosis of the SV to the LRV). |

CV, coronary vein; EP, extended pancreatectomy; IMV, inferior mesenteric vein; LDH, lactate dehydrogenase; LGV, left gastric vein; LOV, left ovarian vein; LRV, left renal vein; PP, partial pancreatectomy; PV, portal vein; RGEV, right gastroepiploic vein; RGV, right gastric vein; SMV, superior mesenteric vein; SV, splenic vein; TP, total pancreatectomy.

this vascular reconstruction might be restricted to highly qualified hospitals. Due to pilot design of the study, few numbers of patients will be enrolled in the current survey, and low sample size can be considered as another limitation of the study.

## Trial's status

This study will be initiated on 01 June 2021.

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