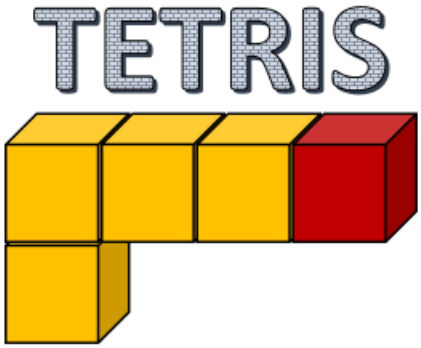
Total pancreatectomy or high-risk pancreatic anastomosis after pancreatoduodenectomy (TETRIS): a randomized controlled trial



Total pancr**E**a**T**ectomy or high-**R**isk anastomos**IS**

Version 3, 04/10/21
Trial: TETRIS (Total pancrEaTectomy or high-Risk anastomosIS)
Sponsor: Università degli Studi di Verona
Clinical Center: Department of General and Pancreatic Surgery
Coordinator: Giovanni Marchegiani
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ABBREVIATIONS

DGE= delayed gastric emptying
ETS= external transanastomotic stent
FRS= fistula risk score
HR-PD= high-risk pancreatoduodenectomy
IPMN= intraductal papillary mucinous neoplasm
NGT= nose gastric tube
PD= pancreatoduodenectomy
PDAC= pancreatic ductal adenocarcinoma
PJ= pancreaticojejunostomy
POD= postoperative day
POPF= postoperative pancreatic fistula
PPH= post-pancreatectomy hemorrhage
QoL= quality of life
TP= total pancreatectomy

INTRODUCTION

Postoperative pancreatic fistula (POPF) is the main driver of surgical morbidity after pancreatoduodenectomy (PD).

Several score systems have been proposed in order to intraoperatively stratify patients based on their risk of developing POPF, allowing a risk-adjusted approach to the reconstructive phase of PD.[1 2] The fistula risk score (FRS) is the most used and extensively validated, and it is based on predictors such as pancreatic parenchyma texture, presumed pathology, main pancreatic duct diameter and estimated intraoperative blood loss (EBL). This prognostic score is able to identify a high-risk cohort (FRS 7-10) representing about 10% of all PDs and having an increased rate of POPF (around 30% and up to 40% in the FRS 10 patients) and consequently worse postoperative outcomes with a major postoperative morbidity around 35%.[3,4] Recently, a large multi-institutional retrospective study and a randomized controlled trial both identified an optimal combination of therapeutic strategies able to mitigate the incidence and the burden of POPF in high-risk patients. Those "mitigation strategies" were the use of externalized trans-anastomotic stent (ETS), pancreatico-jejunal anastomosis (PJ), drains placement and the omission of prophylactic octreotide. [4 5] However, both morbidity and mortality rates after high-risk PD (HR-PD) remain extremely high, even after the implementation of the above-mentioned strategies.[5] Due to its clinical burden, POPF is still associated with delays (> 8 weeks) or omission of adjuvant therapy in two-thirds of complication-bearing patient. [4]

Given the increased postoperative burden of high-risk PDs, total pancreatectomy (TP) might be advocated for those who are at a high-risk for POPF, especially after recent studies showing improved postoperative outcomes of TP at high-volume centers. Stoop et al. found that the historic major postoperative morbidity of 34% after TP decreases to 23% when considering only the most recent years, similarly to another bicentric study including patients undergoing TP from 2000 to 2014.[6 7] A more recent multicenter snapshot study, including TP performed at both high- and low- volume centers between 2018 and 2019, showed a major morbidity of 25% and an in-hospital mortality of 5%.[8] Moreover, recent studies have reported improved postoperative quality of life (QoL) after TP compared to the past, presumably due to centralization at high-volume centers and development of long-acting insulin and modern pancreatic enzyme preparations.[6 9 10 7]

Given the encouraging postoperative outcomes after TPs at high-volume centers, we conducted a retrospective analysis of all PDs and TPs performed at the Verona Pancreas Institute from July 2017 to December 2019 to evaluate TP as an alternative to PD in patients at high risk for POPF development.[11] Albeit the extensive application of the currently recognized mitigation strategies in the HR-PD group, including the use of externalized pancreatic stent and jejunostomy, patients who underwent TP exhibited comparable mortality (3% vs 4%, p= 0,6) and strikingly better postoperative outcomes. In the HR-PD group, the rates of abdominal fluid collection, PPH, DGE, and LOS were nearly doubled, and the rate of sepsis was three times higher than those in the TP group. Major morbidity defined as Clavien-Dindo ≥ 3 was 1,5-fold higher in the HR-PD group (19% vs 31%; p= 0,05). Additionally, cancer- and pancreas- specific QoL seemed to be comparable, while endocrine insufficiency and insulin-dependent diabetes occurred in the totality of patients after TP and TP was associated with worse diabetes-specific QoL. Furthermore, we identified a small cohort of patients (FRS 9-10) at extremely high-risk for POPF (60%) and major morbidity (55%).

This retrospective analysis suggests a role for TP after PD in selected patients at extremely high-risk for POPF after adequate counselling. For the sake of making progress in the management of the pancreatic remnant in high-risk scenario, we firmly believe that these findings need to be confirmed in a randomized fashion.

AIM OF THE STUDY

In patients at extremely high risk for POPF and related severe complications, TP may represent a potential rescue strategy to avoid the morbidity related to the pancreatic anastomosis.

The aim of the present study is to compare TP and primary pancreatic anastomosis (PA) in a cohort of extremely high-risk patients.

OBJECTIVES

PRIMARY OBJECTIVE

To evaluate whether TP is superior to PA in reducing major morbidity, defined as Clavien-Dindo ≥3, in patients with extremely high-risk pancreas.

SECONDARY OBJECTIVES

- To evaluate the incidence and severity of general and pancreas-specific (POPF, postoperative pancreatitis, DGE, PPH, sepsis) postoperative complications and mortality in each group
- To evaluate time to functional recovery and length of hospital stay (days) in each group
- To evaluate the incidence and severity of postoperative endocrine and exocrine insufficiency in each group
- To evaluate the access to adjuvant chemotherapy (when indicated)
- To evaluate cancer-specific, pancreas-specific, and diabetes-related QoL in each group

MATERIAL AND METHODS

The study will be organized as a multicentric randomized controlled trial. When a patient will be considered eligible preoperatively, he or she will be enrolled in the present study.

The patient's risk will be allocated intraoperatively after the demolitive time and before pancreatic anastomosis, according to the following criteria:

Major Criteria
Main pancreatic duct diameter ≤3mm
Soft pancreas
Minor Criteria
Bleeding stump
Friable stump
Posterior/Eccentric duct
Invisible duct
Deep pancreas
Intraoperative acute pancreatitis
FRS 9-10
Interobserver agreement
≥2 Surgeons

Table 1 Eligible patients will have two major and one or more minor criteria confirmed by at least two surgeons

Patients presenting with all major criteria (stage D according to Schuh et al.[12]) and at least one among the minor criteria will be considered eligible. At least two surgeons must confirm eligibility, according to interobserver agreement regarding the above-mentioned criteria and ethical applicability of randomization (ethical "guarantor"). Eligible patients will be randomized to receive PA or TP.
Pre-operative, intra-operative and post-operative data will be recorded prospectively by the P.I. and by his collaborators.

Population

Inclusion criteria

Preoperative

- Patients older than 18 years
- All patients scheduled for PD for all kind of pancreatic diseases
- Patients able to give their informed consent

Intraoperative

- Patients undergoing PD (Kausch-Whipple or Longmire-Traverso)
- Patients presenting two major and at least one minor criteria (Table 1)
- Two or more surgeons confirming eligibility
- PA or TP with or without spleen preservation (Kimura technique). These techniques are consistent with clinical practice; any other procedure will be a deviation from the protocol

Surgical techniques different from those mentioned in the section "procedures" will be considered as a violation of the current protocol.

Drop-out criteria

Preoperative

- Informed consent withdrawal
- Impossibility to undergo surgery for any reason
- Main pancreatic duct of the pancreatic neck/body >3mm at preoperative imaging (CT scan or MRI)

Intraoperative

- PD not performed for any reason
- Absence of two major criteria
- Absence of at least one minor criteria
- Absence of interobserver agreement between at least 2 surgeons
- More than 1 extension of resection to pancreatic neck due to pancreatic margin positivity

Postoperative

- Wrong randomization

Procedures

Preoperative care

Preoperative care will follow institutional standards, according to each center involved. After obtaining the informed consent for elective pancreatic resection and after adequate counselling, the study will be proposed to the patient. Patients with a main pancreatic duct of the pancreatic neck/body >3mm at preoperative imaging (CT scan or MRI) will be excluded. If the patient will accept, the informed consent will be obtained. The physician who will get the informed consent for the procedure will also be responsible for the consent

to the study. Randomization lists will be provided for each Center and for each randomized group. All patients will be preoperatively checked for diabetes by measuring fasting blood glucose (FBG) and Hb1Ac, C- peptide, and for pancreatic exocrine insufficiency by associated clinical criteria and fecal elastase-1 (FE-1) determination.

Intraoperative setting

The resection phase will be carried out according to clinical practice at each participating center. At the time of pancreatic anastomotic reconstruction, the risk will be calculated on the basis of the presence of major and minor criteria (see Table 1):

- The operating surgeon will assess pancreatic texture by manual palpation (only the distinction between "hard" and "soft" is allowed; the expert pancreatic surgeon manual palpation represents the gold standard for pancreatic texture assessment)[13]
- The operating surgeon will precisely measure the main pancreatic duct caliber in millimeters
- The operating surgeon will assess other risk features related to the pancreatic remnant such as: presence of bleeding, friable or deep pancreatic stump[14] ; presence of invisible, eccentric or posterior main pancreatic duct; presence of intraoperative pancreatitis; FRS 9 or 10[1]
- The operating surgeon will confirm the presumed pathology and estimated blood losses will be assessed in order to calculate the FRS

The operating surgeon will decide whether the patient can be included in the study or must be excluded for the presence of any drop-out criteria (see above). The interobserver agreement of at least another surgeon will serve as a confirmation for the inclusion in the trial (ethical "guarantor"). According to the presence of two major and one or more minor criteria patients will be included in the study and randomized in two groups. A picture of the pancreatic remnant will be taken intraoperatively before anastomosis/totalization. Both patients undergoing open and minimally invasive surgery can be considered eligible.

PA Group

PA will be carried out according to the techniques adopted by the participating Centre, either pancreatico-jejunostomy (PJ) (i.e. dunking PJ, Cattel-Warren duct-to-mucosa PJ, Blumgart PJ) or pancreatico-gastrostomy (PG) will be considered eligible. Any mitigation strategy (i.e. ETS, use of glues/biological matrices to protect the anastomosis, surgical feeding jejunostomy, prophylactic hydrocortisone/somatostatin administration) can be used according to the Center practice. The other two anastomosis, hepaticojejunostomy and duodenojejunostomy (in case of Longmire-Traverso PD) or gastrojejunostomy (in case of Kausch-Whipple PD), will be carried out as usual according to each Institution's operative standards.[15]

At least one surgical drain will be placed in the retroperitoneum in all patients.

TP Group

TP will be carried out according to each Institution's operative standards. Preservation of the spleen will be considered whenever possible according to Kimura technique. Either ligation or preservation of gastric vessels (right/left gastric artery/vein) will be allowed according to clinical necessity but will be recorded and correlated with postoperative outcomes.[16]

The reconstruction phase will be carried out according to each Institution's operative standards. One or more surgical drains can be left in place according to surgeon's preference.

Postoperative care

After the procedure, the patient will be admitted to the ICU or in the ward. The management of intravenous fluids, nasogastric tube, bladder catheter and postoperative analgesia will take place as usual according to

each Institution's standards of care. In the PJ Group, the amylase value of drain fluids will be checked on POD1, POD3 and at any POD if it will help to diagnose a still undiscovered POPF. Surgical drain will be managed according to clinical judgment and each Institution's clinical standards. During hospitalization, all patients will receive specialistic evaluation to assess and possibly treat the occurrence of new onset diabetes or the worsening of pre-existing diabetes. Pancreatic exocrine insufficiency will be treated with oral supplementation of pancreatic enzymes if needed. Patients in the TP Group will be vaccinated 1 month after complete functional recovery against Pneumococcus, Hemophilus influenzae group B, and Meningococcus to minimize the likelihood of developing post-splenectomy sepsis. All patients will receive an outpatient follow-up, 1 month after discharge and every 6 months for 2 years. During follow-up, glycemic control, nutritional status, and possible symptoms of exocrine insufficiency will be assessed, and patients will receive specialistic assistance if needed. QoL will be registered using specific questionnaires. An oncologic evaluation will determine the indication for administration of adjuvant therapy, in case of malignancy.

Questionnaires

All patients who will be alive after at least 12 months of follow-up will be enrolled in the cross-sectional study of quality of life. All the eligible patients who are not able to attend outpatient visits will be contacted by telephone before receiving the 5 questionnaires by mail. Patients who will not respond within 1 month will be contacted again by telephone. Four questionnaires will be administered: (1) the EuroQoL Group questionnaire (EQ-5D); (2) the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire; (3) the European Organization for Research and Treatment of Cancer (EORTC) QLQ-PAN26 questionnaire; and (4) the Problem Areas in Diabetes (PAID) questionnaire.[17] [18] [19] [20] The comprehensive assessment will consist of a total of 116 questions.

ENDPOINTS

Primary endpoint

For each study group the primary endpoint is the rate of postoperative major morbidity, defined as Clavien-Dindo≥ 3.

Secondary endpoints

For each study group secondary endpoints are:

- Incidence of In-hospital, 30-days and 90-days postoperative mortality. Beyond these time-limits, the mortality that may be related to the operation will be considered and discussed in each case.
- Incidence, severity, and overall average complication burden for PPH and DGE
- Incidence of other postoperative morbidity (see below)
- Time-to-functional recovery (functional recovery is defined by all of the following criteria: adequate pain control with only oral analgesia (no intravenous or epidural analgesia necessary); independent mobility; ability to maintain more than 50% of the daily required caloric intake; no need for intravenous fluid administration; and no signs of infection)[21]
- Length of hospital stay
- Postoperative endocrine insufficiency (new onset diabetes, worsening of pre-existent diabetes, insulin dependency). The definition of postoperative new onset of diabetes will be based on the reporting of a normal preoperative FBG/HbA1c and postoperatively by measured glucose metabolism including FBG/HbA1c level and/or insulin medication.
- Postoperative exocrine insufficiency (incidence of diarrhea, prescription of pancreatic enzymes, number of capsules). The definition of postoperative exocrine insufficiency will be based on FE-1

determination, the presence of steatorrhea and necessity of enzyme treatment with cessation/mitigation of diarrhea after enzyme supplementation.
- Access to adjuvant chemotherapy (when indicated)
- Delay in starting adjuvant chemotherapy, calculated as the time between surgery and the beginning of adjuvant chemotherapy (when indicated)
- General, cancer-specific, pancreas-specific and diabetes-related QoL (EQ-5D; EORTC QLQ C30 and PAN26; PAID) [17] [18] [19] [20]

The observation period for postoperative morbidity will last until the complete recovery from surgery. Morbidity will include:
- PPH as defined by ISGPS [22]
- DGE as defined by ISGPS [23]
- Bile leakage as defined by ISGLS[24]
- Enteric fistula defined as presence of enteric fluid from drains, possibly confirmed by sinogram or plain radiography with oral contrast study
- Abdominal fluid collection defined as any intraabdominal fluid collections larger than 5cm confirmed at imaging
- Abdominal abscess defined as an intraabdominal fluid collection containing gas bubbles and producing clinically relevant signs of infection
- Wound infection as defined by CDC [25]
- Blood transfusions defined as the number of packed red blood cells unit transfused after the procedure
- Sepsis [26]
- Chyle leak as defined by ISGPS [27]
- Gastric venous congestion [16]
- Postoperative liver failure
- Myocardial infarction
- Acute kidney injury
- Pulmonary embolism
- Pneumonia
- Respiratory distress (defined as the need for mechanic ventilation after surgery)
- Urinary tract infection
- Neurological morbidity (cerebrovascular accidents, hemorrhage)
- Re-operation
- Re-admission within 30, 60 and 90 days

For PA Group additional secondary endpoints are:
- Incidence and severity of POPF [28]
- Incidence of biochemical leak [28]
- Overall average complication burden for POPF
- Incidence of postoperative pancreatitis [29]

SAMPLE SIZE CALCULATION

A recent metanalysis by Schuh et al. reported a POPF rate around 23% in stage D patients (main pancreatic duct diameter ≤3mm, soft pancreas) but no data were available regarding major morbidity[12]. Patients that will be considered eligible for the present trial will have further features increasing their risk of POPF and

related major morbidity, compared to stage D patients. Based on the current literature and on a recent retrospective study by the Verona group, considering only a cohort of patients with extremely high FRS (FRS 9-10), the rate of major morbidity can be estimated around 55% after PD and 19% after TP.[11]
The original risk score proposed in this trial is extrapolated based on previous literature and expert opinions. For this reason, there are no data directly available for estimation of major morbidity in this rare subset of patients, for which we estimate a rate of Clavien-Dindo ≥3 of around 40%.
Considering a 1:1 allocation between the groups, a sample size of 49 patients per group would allow a two-sides, two-sample test for binomial proportions to detect a difference in Clavien-Dindo ≥3 of 25% (40% vs 15%) with 80% power (1-β) and an error α of 0,05. The study has a group sequential design allowing for interim analyses at pre-specified timepoints with possible early stopping for efficacy or futility in case of an overwhelming large or small effect, respectively. Considering that extremely high-risk cases represent around 7% of the total amount of PDs performed and that the fistula risk can only be assessed intraoperatively, we expect to approach preoperatively around 1300 patients.

STATISTICAL ANALYSIS

Continuous variables will be expressed as the means and standard deviation values or as median values with ranges and will be compared using the Student t-test or the Mann-Whitney test as appropriate. Categorical variables will be analyzed by Chi-square or Fisher's exact test in case of expected small frequencies. All the tests will be 2-tailed. P values < 0.05 will be considered statistically significant. All endpoints will require the above-mentioned statistical analysis, comparing the two study arms. Statistical analyses will be performed using STATA14 for Windows.

DURATION AND END OF THE STUDY

Since the Department of General and Pancreatic Surgery performs about 250 PD per year and the study will be proposed to at least other 2 international referral centers, the primary endpoint will be reached after 25 months: 22 months of patients' enrollment and 3 months of follow-up. Long term analysis of QoL and pancreatic insufficiency will require additional 24 month of follow-up. Time for data analysis must be considered negligible. All the patients undergoing PD will be enrolled for the study if inclusion and exclusion criteria will be respected. The study will be discontinued in case of reaching the statistical significance of the primary endpoint, or in case of suspension by the coordinators or by the authorities.

PROCEDURES RELATED TO REGISTRATION AND DATA MANAGEMENT

To ensure the confidentiality of data, each patient will be registered and de-identified by an identification code.
Each subject will be identified by a code consisting of:

- Code Protocol: TETRIS
- Number of the institution: (e.g. Patient recruited at the Verona Pancreas Institute will be coded as TETRIS_C1)
- Number of recruitment (e.g. the third patient recruited at the Verona Pancreas Institute will be coded as TETRIS_C1_3).

The P.I. of the study will be responsible for data protection and privacy of study participants by treating the data solely for statistical purposes and scientific research, and he will not communicate them if not anonymously. The manager of data processing is the principal investigator.
All data of enrolled patients collected during the study will be recorded in a computerized case report form (CRF) and transferred automatically into a specific database protected by passwords. These data will be kept confidential and will be treated in full compliance with the Legislative Decree 196/03.

ETHICAL CONSIDERATIONS

Each patient will be included in the study only after providing his/her written informed consent, which may be withdrawn at any time. Personal data will be processed according to Legislative Decree 196/2016. The procedures relating to the conduct of the study and documentation of the results shall comply with ethical principles set out in the Declaration of Helsinki, in the Oviedo Convention and Good Clinical Practice. The study will be conducted in compliance with following documents: European Directive 91/507 / EEC, Decree 211/03, D.M. December 21, 2007, AIFA Determination March 20, 2008, D.L. 189 of 08/09/2012, European Directive 2011 / C172 / 01 and Decree 196/2016. The evaluation of the study is responsibility of the Ethics Committee and its implementation will be possible only after its approval. Any amendment to the Protocol will follow the same approval process.

QUALITY OF THE STUDY, GOOD CLINICAL PRACTICE AND ETHICS COMMITTEE

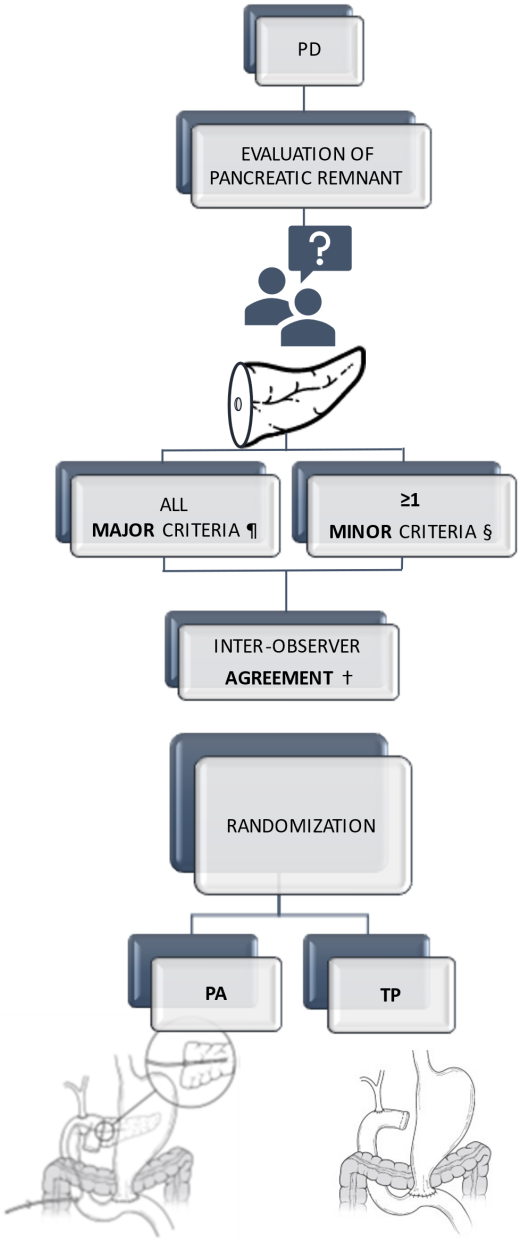
The procedures relating to management, implementation and documentation of the study will be in accordance with the ethical principles set out in the Helsinki Declaration and its revisions, the Oviedo Convention, the GCP (Good Clinical Practice). The evaluation of this study is responsibility of the Ethics Committee that will be informed of any possible subsequent revision of the protocol. After the approval of the local Ethics Committee, the study will be entered in the international registers (clinicaltrials.gov).

FLOWCHART

TETRIS

Total pancrEaTectomy or high-Risk anastomosIS

¶ MAJOR
• Main Pancreatic Duct ≤3mm • Soft Pancreas
§ MINOR
• Bleeding stump • Friable stump • Eccentric duct • Posterior duct • Invisible duct • Deep pancreas • Intraoperative AP • FRS 9-10
† AGREEMENT
• ≥2 Senior Surgeons



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