Preoperative radiotherapy in patients at very high risk of postoperative pancreatic fistula after pancreatoduodenectomy (FIBROPANC): a multicenter phase II study

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shared senior

Netherlands Trial Register 72913

METC number NL72913.018.20

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PROTOCOL TITLE “Preoperative radiotherapy in patients at very high risk of postoperative pancreatic fistula after pancreatoduodenectomy (FIBROPANC): a multicenter phase II study”

Protocol ID	Trial register number: 72913
Short title	FIBROPANC
EudraCT number	Not applicable
Version	3.0
Date	11-08-2022
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Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
CT	**Computerized tomography**
CTV	**Clinical target volume**
DPCA	**Dutch Pancreatic Cancer Audit**
DSMB	**Data Safety Monitoring Board**
ERCP	**Endoscopic retrograde cholangiopancreatography**
EU	**European Union**
EUS	**Endoscopic Ultrasound**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
Gy	**Gray**
IC	**Informed Consent**
ICU	**Intensive care unit**
MDT	**Multidisciplinary team**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MR	**Magnetic Resonance**
POPF	**Postoperative pancreatic fistula**
PPPD	**Pylorus preserving pancreatoduodenectomy**
PRPD	**Pylorus resecting pancreatoduodenectomy**
PTV	**Planning target volume**
SAE	**Serious Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical**

	company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Postoperative pancreatic fistula (POPF) is a potential life-threatening complication after pancreatoduodenectomy. POPF is caused by an anastomotic dehiscence of the pancreato-jejunostomy or pancreato-gastrostomy created in the reconstruction phase of a pancreatoduodenectomy (i.e. Whipple) procedure [1]. It occurs in approximately 15% of all patients undergoing pancreatoduodenectomy and is the primary cause of complications after this procedure, associated with increase in length of hospital stay, radiological or surgical interventions, higher readmission rates, higher costs and even death in up to 25-30% of patients with POPF [2-4]. Soft pancreatic texture, small pancreatic duct diameter, high BMI and male sex are well-known risk factors for the development of POPF [5, 6]. Furthermore, patients undergoing pancreatoduodenectomy for diagnoses other than pancreatic ductal adenocarcinoma have a higher risk of POPF [4, 7]. These diagnoses include: distal cholangiocarcinoma, duodenal carcinoma, ampullary carcinoma, pancreatic neuroendocrine tumor, intraductal papillary mucinous neoplasm (IPMN), or premalignant lesions in the periampullary region. In patients with a tumor of the peri-ampullary region and a narrow pancreatic duct diameter, the risk of developing a pancreatic fistula is even over 25%. The recent Dutch multicenter PREOPANC trial found significantly less POPF after pancreatoduodenectomy in patients with pancreatic cancer who had undergone neoadjuvant chemoradiotherapy as compared to patients with upfront surgery [8]. This finding is supported by other studies [9-11]. The hypothesis is that radiotherapy leads to fibrosis which is hardening the pancreatic tissue, hereby decreasing the risk of POPF.

In the current study, we hypothesize that a single course of 12Gy preoperative radiotherapy may lead to sufficient fibrosis in a small (4cm) targeted area of pancreatic tissue where the anastomosis with either the jejunum will be created, thereby reducing the risk of grade B and C POPF in patients at high risk of developing this complication after pancreatoduodenectomy.

Objective: To investigate the feasibility and safety of preoperative stereotactic radiotherapy of 4cm pancreas in patients undergoing pancreatoduodenectomy at high risk (>25%) of developing POPF.

Study design: Multicenter open-label single-arm phase II study.

Study population: Adult patients scheduled for pancreatoduodenectomy for malignant and premalignant periampullary tumors, excluding pancreatic adenocarcinoma, with a pancreatic duct diameter ≤ 3 millimetres. In the first 20 patients, safety will be determined as well as an objective measurement of pancreatic texture using a durometer. If both safety and feasibility are met in the first 20 patients then, 13 more patients will be included to provide a reliable estimate of the rate of POPF. These additional 13 patients are required to more reliably determine the need for a future randomized controlled trial.

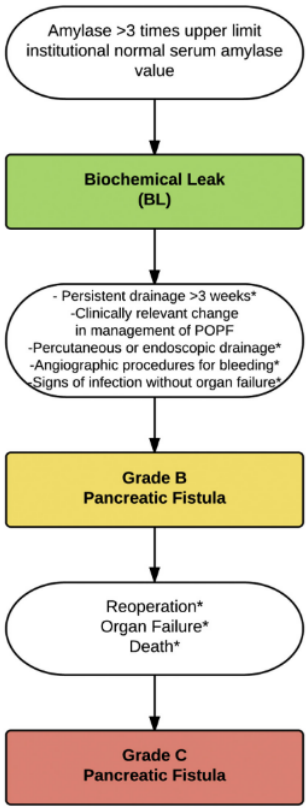
Intervention: Preoperative radiotherapy delivered in a single fraction of 12 Gy focussed on 4cm pancreas at the intended (i.e. future) anastomotic site.

Main study parameters/endpoints:
Safety (maximum of 3 patients with CTCAE grade 3-4-5 complications) and efficacy (significant change in the within-patient durometer measurements of radiated and non-radiated pancreatic texture) of preoperative radiotherapy. Hereafter, if both criteria for safety and efficacy are met, the endpoint POPF Grade B and C is assessed in 13 more patients, totalling 33 patients.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients will undergo an outpatient clinical visit at the radiation oncology department to discuss the radiotherapy. In addition, they will receive a planning CT scan (or MR-scan) in treatment position before the start of radiotherapy. Treatment itself is delivered in a single fraction in one day. Subacute and late effects following a single fraction of 12 Gy are expected to be limited and can consist of gastrointestinal toxicity (nausea, diarrhoea). Although radiotherapy can be associated with a small increased risk of secondary cancers, typically affecting organs adjacent to the irradiated area, this risk can be neglected for the single doses used for this study. First because, using these modern techniques of radiotherapy, no adjacent organs are in the radiation field. Secondly, given the fact that the prognosis of the patients is largely determined by their primary tumor and the preoperative radiotherapy of the pancreatic remnant has a protective effect in preventing mortality.

1. INTRODUCTION AND RATIONALE

Postoperative pancreatic fistula (POPF) is defined by the International Study Group (ISGPS) as an anastomotic dehiscence of the pancreato-jejunostomy or pancreato-gastrostomy anastomosis in the reconstruction phase of a pancreatoduodenectomy (i.e. Whipple) procedure [1]. POPF is the most common potential life-threatening complications after pancreatoduodenectomy and occurs in approximately 15-20% of patients [3, 4]. The diagnosis can be confirmed by drain output containing >3 times the upper limit of normal amylase on or after postoperative day 3 in combination with a clinical intervention or prolonged (3 weeks) drainage via the peroperatively placed surgical drain. The leakage of the aggressive enzyme-rich pancreatic fluid combined with small amounts of bowel content into the intra-abdominal space may lead to sepsis and bleeding which are lethal in up to 30% of patients [2-4]. POPF often results in the need for radiological or surgical interventions, admission to an intensive care unit (ICU), increase in length of hospital stay, higher readmission rates, and higher costs [2]. The severity of POPF is graded based on the clinical impact (Fig 1.), a biochemical leak (i.e. formerly defined as 'Grade A' POPF) being the mildest form with no clinically relevant impact on the patient. Grade B and C are considered clinically relevant because of the severe impact on the patient due to the need for interventions, organ failure and even death.



Treatment/Event POPF related

Fig 1. Bassi et al. Surgery 2017. Flow chart for biochemical leak and postoperative fistula grade definition

Soft pancreatic texture, small pancreatic duct diameter, high BMI and male sex have been identified as risk factors for the development of POPF [5, 6]. Furthermore, patients undergoing pancreatoduodenectomy for diagnoses other than Pancreatic Ductal adenocarcinoma have a higher risk of POPF [4, 7]. These diagnoses include: distal cholangiocarcinoma, duodenal carcinoma, papil carcinoma, pancreatic neuroendocrine tumor, intraductal papillary mucinous neoplasm (IPMN), or benign lesions in the periampullary region. The recently completed Dutch multicenter PREOPANC-1 trial found significantly less POPF after pancreatoduodenectomy in patients with pancreatic cancer treated with neoadjuvant chemoradiotherapy compared to patients with upfront surgery [8]. This finding is supported by other studies [9-11]. An explanation can be that chemoradiotherapy decreases the risk of POPF because of the development of fibrosis in post-radiation pancreatic tissue. Radiation-induced fibrosis is characterized by tissue reorganization and immune response modulation due to the accumulation of various cells (i.e. fibroblasts and inflammatory cells) and extracellular matrix proteins, such as collagen, resulting in scar formation [12]. The development of fibrosis in the normally soft and vulnerable pancreatic tissue could create support at the site of the pancreato-enteral anastomosis by hardening the pancreatic tissue. Currently, neoadjuvant chemoradiotherapy is only indicated for patients undergoing pancreatoduodenectomy for pancreatic cancer. Analysis of data collected in the prospective nationwide Dutch Pancreatic Cancer Audit (DPCA) for pancreatic surgery show a significantly lower amount of clinically relevant grade B and C POPF in patients undergoing pancreatoduodenectomy for pancreatic carcinoma compared to patients undergoing pancreatoduodenectomy for other indications (8% versus 20%, $p<0.01$). Other indications for pancreatoduodenectomy include patients with distal cholangiocarcinoma, duodenal carcinoma, Papil of Vater carcinoma, pancreatic neuroendocrine tumor, intraductal papillary mucinous neoplasm (IPMN), or premalignant lesions in the periampullary region. In the group with a pancreatic duct diameter of ≤ 3 millimetres, the incidence of developing grade B or C POPF is even 27%. These patients are now identified as the “high risk” patients of developing a clinically relevant POPF. To objectively assess pancreatic texture, several Durometers have been used [13-15]. Results for the Rex Gauge Durometer (ranging from 0 to 100) were significantly lower in soft pancreatic tissue (median 11, IQR 8-13) compared to hard pancreatic tissue (median 25, IQR 21-28) ($P < 0.001$)[13]. Another way to quantify fibroses is via digital image analysis in histopathology, determining the area of collagen using Sirius red [16, 17].

In the current study, we aim to perform a feasibility study for our hypothesis that a single dose of preoperative radiotherapy of 12 Gy targeted at 4cm pancreas containing the future anastomotic site may induce local fibrosis of this pancreatic tissue, thereby potentially reducing

the amount of POPF in patients with a very high risk of developing POPF (>25%), following pancreatoduodenectomy.

2. OBJECTIVES AND ENDPOINTS

Primary objective: to determine the safety and feasibility of a single dose preoperative radiotherapy prior to pancreatoduodenectomy in patients at very high risk of grade B/C POPF.

Main secondary objective: rate of grade B/C POPF.

The secondary endpoints are

- Percentage of patients with biochemical leak, postoperative fistula Grade B or C, defined by the ISGPS guideline (2016).
- Fibrosis in the histopathology, measured as the percentage of collagen in the pancreatic resection margin and compared to fibrosis in the pancreatic head (not the resection margin) of the same patient.
- Pancreas texture, determined intraoperatively by the pancreatic surgeon:
    - does the pancreatic tissue feel different at the radiotherapy location in comparison to the pancreatic tail and pancreatic head (both away from the 4cm radiotherapy site).
- Surgeon impression*:
    - Do you have the impression that radiotherapy caused local fibrosis of the pancreatic texture in this patient? a)Yes, b)Unclear, c)No.
- Macroscopic assessment:
    - Was fibrosis present at the pancreatic resection margin? a) No b) Yes. If yes: level of fibrosis: a) Mild b) Moderate c) Severe
- Other pancreatic-surgery-related postoperative complications as defined by the ISGPS guidelines.
- Surgery related postoperative complications defined according to the Clavien-Dindo classification.
- Overall complications.
- Length of hospital stay in days.
- Readmission rate.
- 30-day mortality and in-hospital mortality.
- Pancreatic endocrine function (blood glucose) and exocrine function (faecal elastase)

*The ‘surgeon impression’ endpoint aims to determine smaller differences that detected with the rough score normal/soft vs hard/fibrotic

3. STUDY DESIGN

The study will be a multicenter open-label single-arm phase II clinical study.
The first part of the study will be performed in order to establish safety and feasibility radiotherapy administration before pancreatoduodenectomy in 20 eligible patients. When both criteria for safety and feasibility are met, the second part of the study will start, including 13 additional patients (totaling 33 patients) to provide a reliable estimate of the rate of grade B/C following this intervention. The latter will be used to determine the need for a multicenter randomized controlled trial.

First part: Safety/feasibility
The main goal of the first inclusion part is to determine safety of radiotherapy before pancreatoduodenectomy in 20 patients according to Common Terminology Criteria for Adverse Events (CTCAE version 5). All grade 3-5 events potentially related to the preparation (e.g. endoscopic fiducial marker placement) or administration of radiotherapy will be considered events for this endpoint. The study is defined safe/feasible when ≤ 15% of the 20 patients experience a grade 3-5 toxicity, meaning a maximum of 3 patients. The rationale for the 15% comes from the intended benefit of a reduction from 25% to 10% (15% reduction) of grade B/C POPF. The adverse event rate should not be higher than the intended benefit. Feasibility is determined when a significant difference is measured in the aspect of the radiated part of the pancreas, compared to the non-radiated part of the pancreas (head of the pancreas; so in total 2 measurements in every patient) using the digital Rex Gauge Durometer, Model DD-4 Digital Durometer Type OO [13, 18]. The Durometers measurement will be obtained via ex vivo measurements on a back-table in the operating room.

Second part: efficacy
In the second part, an additional 13 patients will be included in order to determine the clinical efficacy of radiotherapy in terms of grade B/C POPF with enough confidence to advise on a potential future multicenter randomized controlled trial. All included patients (n = 33) will be analysed for this endpoint.

Given the yearly number of patients eligible for this study in the participating high volume pancreatic centers, the expected inclusion period will be 24-28 months.

After first consultation with the treating physician, eligible patients will be asked if they are interested in participating in this clinical trial. They will be provided with spoken and written information and will get the time to consider the patient information and ask remaining

questions before giving informed consent. When informed consent has been signed, patients will be planned to undergo radiotherapy. In preparation for treatment delivery, all patients will undergo a planning-CT scan, or a planning-MRI in case of MR-guided treatment. Patients will be simulated and treated in supine position. Radiotherapy treatment will be performed in hospitals using stereotactic ablative radiotherapy (SABR). In hospitals where radiotherapy is delivered using Cyberknife radiation will be performed using the Internal Target Volume (ITV). A single dose of 12 Gy radiotherapy will be delivered at the intended location of the pancreato-jejunal anastomosis. After radiotherapy, pancreatoduodenectomy will follow after 4-6 weeks. The total number of included patients in both parts (n=33) will be followed up as per standard of care after ending their treatment period and analyzed for all endpoints given in chapter 2.

4. STUDY POPULATION

4.1 Population (base)

Eligible patients are scheduled to undergo pancreatoduodenectomy for another indication than pancreatic ductal adenocarcinoma with a pancreatic duct diameter ≤ 3 millimetres.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

- Patients scheduled to undergo pancreatoduodenectomy for another indication than pancreatic ductal adenocarcinoma.
- Pancreatic duct diameter ≤ 3 millimetres, measured on the diagnostic CT scan (at the level of the portomesenteric vein, at the pancreatic neck, the future anastomotic site).
- WHO-ECOG performance status 0,1 or 2.
- Ability to undergo stereotactic radiotherapy and surgery.
- Age ≥ 18 years.
- Good understanding of the oral and written patient information provided.
- Written informed consent.

4.3 Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this study:

- Patients undergoing pancreatoduodenectomy for (suspected) pancreatic cancer, chronic pancreatitis, or benign neoplasms (e.g. serous cyst) in the periampullary region.
- Patients with (a history of) chronic pancreatitis
- Contra-indications for MRI (only for VUmc and UMCU), (e.g. presence of a pacemaker or defibrillator, metal splinters).

4.4 Sample size calculation

The objective is to determine the safety and feasibility of this single fraction preoperative homogeneous stereotactic radiotherapy on 4cm pancreas as well as the potential efficacy of preoperative radiotherapy to diminish the development of POPF.

With a sample size of 20 patients and an expected reduction of 15% in POPF, we can accept at most 3 patients (<15%) with grade 3-4-5 toxicity related to the intervention (stereotactic radiotherapy). Furthermore, for efficacy in 20 patients, a one sample t-test with a 5% one-sided significance level will have 80% power to detect the difference between a null hypothesis mean of 11 and an alternative mean of 25 (on Durometer measurements), assuming that the standard deviation is 21.198 as based on a recent

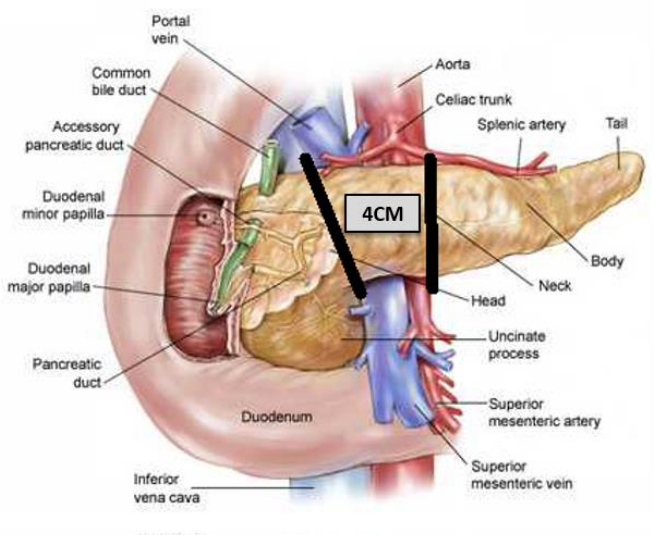
publication [13]. For the second part, focussing on clinical efficacy, using the calculation Sample Size for Phase II Study (Fleming's Procedure), an additional 13 patients are needed to calculate a reduction in POPF from the baseline risk of 25% to 10% (alpha = 0.05, power 0.80), intended 15% reduction. To prevent Type II errors, complete measurements for safety, feasibility and POPF are required in 33 patients. If, due to unforeseen circumstances (not related to intervention) an endpoint cannot be evaluated (e.g. patients does not undergo resection due to discovery of metastases during exploratory laparotomy, or withdrawal of informed consent before the intervention), an additional subject will be included. All patients who have undergone the intervention (SBRT) will remain in the study for follow-up. The expected risk of unforeseen circumstances in the study population is low.

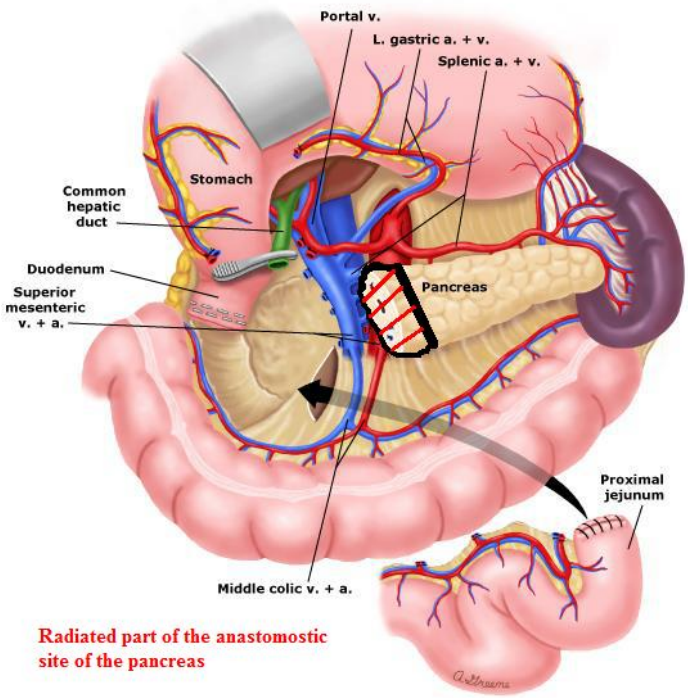
5. TREATMENT

5.1 Diagnostic strategies

When patients are presented with a suspected lesion in the periampullary region in the Netherlands, the diagnostic procedures are based on routine clinical practice, including CT scan and in the absence of a mass an endoscopic ultrasound [19]. All patients are discussed in a multidisciplinary team (MDT). A treatment advise and plan are made and eligible patients will be identified.

5.2 Homogeneous radiotherapy planning with stereotactic precision





5.2.1 Preparations

In preparation for treatment delivery, all patients will undergo a planning-CT scan, or a planning-MRI is performed in case of MR-guided treatment. Patients will be simulated and treated in supine position. In case of treatment in the UMC Utrecht before treatment a custom made abdominal corset is made to reduce abdominal breathing motion. At Erasmus MC a vacuum mattress is customized to limit movement during radiation. Intravenous contrast may be used during simulation; however, it will not be required. Oral contrast should be used with caution as it may interfere with the planning process, and the reproducibility during treatment delivery.

5.2.2 Target volumes CTV, PTV

Gross target volume (GTV): middle of the pancreatic corpus, covering the intended location of the pancreatico-enteric anastomosis: from the right sided border of the portal vein 4cm to the left (i.e. towards the spleen). Planning target volume (PTV) margin will be generated by the addition of a 3-5 mm margin around the GTV depending on institutional protocols.

Cyberknife technology:

The Internal Target Volume (ITV) will be based on the patients free breathing movement. The ITV will be made on the in0% (beginning of inhalation), in50% (middle of inhalation), in100% (end of inhalation) and ex50 (middle of exhalation). The ITV=GTVin0% + GTV in50% + GTVin100% + GTVex50. The margin from ITV to PTV is 5mm.

5.2.3 Treatment planning and Dose prescription

PTV dose prescription: 12 Gy in 1 fraction to the outline of the PTV a cylinder encompassing the pancreatic duct and surrounding circumferential pancreatic tissue.

- $D_{95\%}$ ≥95% of the prescribed dose (95% of the PTV receives at least 95% of the prescribed dose)
- $D_{2\%}$ ≤110% of the prescribed dose (2% of the PTV receives a maximum dose of 110% of the prescribed dose) meaning a homogenous planning.

5.2.4 Toxicity complications

Both early and subacute toxicity will be scored at baseline and at the completion of radiotherapy, conform the Common Toxicity Criteria of Adverse Events (CTCAE) version 5.0, with a special focus on gastrointestinal disorders and fatigue.

5.2.5 Patient advise

- Patients may receive dietary instructions (e.g. treatment will be delivered after 2 hours fasting).
- Patients may be pre-medicated (2 hours before radiotherapy) with ondansetron (1x8 mg)) in order to prevent radiation-induced nausea.

5.3 Surgery

5.3.1 Preparations

All patients will have a preoperative consultation from an anesthesiologist.

5.3.2 Techniques

Pancreatoduodenectomy and anastomotic technique will be performed via the Institutional standard. Both open and minimal invasive surgery may be used. No limitations are provided for anatostomotic technique and minimally invasive vs open surgery since several randomized studies have confirmed that there is no significant difference in the rate of POPF between these options.

5.3.3 Postoperative management

According to the Institutional standard.

5.4 Escape medication (if applicable)

Not applicable.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

6.3 Summary of findings from clinical studies

6.4 Summary of known and potential risks and benefits

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labelling of Investigational Medicinal Product

6.8 Drug accountability

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study endpoint

Primary objective: to determine the feasibility and safety of a single dose preoperative radiotherapy prior to pancreatoduodenectomy in patients at very high risk of grade B/C POPF.

8.1.2 Secondary study endpoints

Main secondary endpoint: rate of grade B/C POPF.

Other secondary endpoints are

- Fibrosis in the pancreatic resection margin as determined by histopathology and compared to fibrosis in the pancreatic head (not the resection margin).
- Pancreas texture, determined intraoperatively by the pancreatic surgeon:
    - does the pancreatic tissue feel different at the radiotherapy location in comparison to the pancreatic tail and pancreatic head (both away from the 4cm radiotherapy site)
- Surgeon impression*:
    - Do you have the impression that radiotherapy caused local fibrosis of the pancreatic texture in this patient? a)Yes, b)Unclear, c)No.
- Macroscopic assessment:
    - Was fibrosis present at the pancreatic resection margin? a) No b) Yes. If yes: level of fibrosis: a) Mild b) Moderate c) Severe
- Individual rate biochemical leak, postoperative fistula Grade B or C, defined by the ISGPS guideline (2017).
- Other pancreatic-surgery-related postoperative complications as defined by the ISGPS/ISGLS guidelines.
- Postoperative complications defined according to the Clavien-Dindo classification.
- Overall complications.
- Length of hospital stay in days.
- Readmission rate.
- 30-day mortality and in-hospital mortality.
- Pancreatic endocrine function (blood glucose) and exocrine function (faecal elastase)

*The ‘surgeon impression’ endpoint aims to determine smaller differences that detected with the rough score normal/soft vs hard/fibrotic.8.1.3 Other study parameters (if applicable)

- Baseline variables: sex, age, BMI, diagnosis

8.2 Randomisation, blinding and treatment allocation

Not applicable.

8.3 Study procedures

All measurements, methods and/or tests used to assess the defined study parameters/endpoints are collected in the standard postoperative care.

8.4 Withdrawal of individual subjects

Subjects can withdraw his or her consent to the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

8.5 Replacement of individual subjects after withdrawal

Reasons for patient replacement:
- Patients who drop out of the study before receiving the intervention, i.e. radiotherapy or placement (Erasmus MC).

8.6 Follow-up of subjects withdrawn from treatment

Following usual care.

8.7 Premature termination of the study

In the unlikely event that a patient suffers a lethal complication from fiducial marker placement, stereotactic radiotherapy or surgery, accrual will be put on hold, and the Trial management group will discuss the matter with the data safety management board in due time. Thereupon will be decided whether or not the study will be closed or amended. Decisions will be communicated with the METC and the sponsor.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to fiducial marker placement or stereotactic radiotherapy. All adverse events classified as CTCAE version 5.0 grade 3 or higher reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Fiducial placement adverse events

Side effects of endoscopic fiducial marker placement are low and are mainly grade 1 complications like bowel cramps and nausea.

Adverse events

- Pancreatitis (if grade ≥4 report as a serious adverse event)
- Cholangitis
- Minor bleeding
- Fever
- Nausea/ vomiting
- Abdominal pain
- Elevated liver enzymes

All episodes of the above mentioned acute and late adverse events from fiducial marker placement will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Radiation induced adverse events

Side effects like fatigue, loss of appetite and nausea can occur. However, severe side effects (grade ≥ 3) and adverse events usually do not occur after low dose radiation therapy.

Adverse events:

- Fatigue
- Loss of appetite
- Nausea/ vomiting
- Stomach ulcers
- Diarrhea

All episodes of the above mentioned acute and late adverse events from stereotactic radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Patients receive acid blockers and analgesics as standard of postoperative care.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

Grade 4 events (that are possibly related to stereotactic radiotherapy or surgery) and all deaths (regardless of attribution) which occurs until 30 days after surgery must be reported via email or telephone within 24 hours after occurrence to the corresponding author (J A Suurmeijer).
Only hospitalisations which require a prolongation of an existing hospitalization of >10 days will be reported.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs

that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Since there are 33 patients included in this feasibility study, no Data Safety Monitoring Board (DSMB) will be established.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

For safety, CTCAE v5.0 events are described as numbers and percentages. Pancreatic texture, measured with the digital Rex Gauge Durometer, be presented with a mean and standard deviation or median with interquartile range for both the radiated and not radiated part of the pancreas and compared using a paired t-test or Wilcoxon signed rank test according to distribution.

Grade B/C POPF as determined by the 2017 ISGPS definition will be described as numbers and percentages and analyzed using a z-test for proportions.

10.2 Secondary study parameter(s)

Descriptive statistics will be used for all secondary endpoints and baseline characteristics. Normally distributed continuous data will be presented as means with standard deviations (SD). Non-normally distributed continuous data will be expressed as medians with interquartile ranges (IQR). Normality of data will be checked by visual inspecting of the histograms and boxplots. Categorical data will be presented in frequencies with percentages

10.3 Other study parameters

Not applicable

10.4 Interim analysis (if applicable)

No formal interim analysis will be done

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (version October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

The treating physician will inform eligible patients about the study and will explain the aims, methods, anticipated benefits, and potential hazards. Also, this information will be provided in print. Subsequently, patients will have at least 48 hours to decide if they want to participate in the study, by giving their written informed consent. Written informed consent is required before any study related procedures takes place. If patients have any further questions they can also consult an independent physician.

The investigator shall provide a copy of the information sheet and the signed consent form to the patient and the signed original shall be maintained in the Investigator File.

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

Patients participating in this study may experience side effects as defined in section *9.2.1 Adverse Events.* However, we expect that subacute and late effects following a single fraction of 12 Gy will be limited, especially given the potential effect of preventing POPF and postoperative mortality.

11.5 Compensation for injury

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

When informed consent has been signed, patients obtain a study number (FIB01-FIB20). As long as it is necessary to be able to trace data to an individual subject, a subject identification code list will used to link the data to the subject. The key to the code is safeguarded by the investigator. All data collected will be stored in a secured database and is in accordance with the Dutch Law Algemene verordening gegevensbescherming (AVG). The database will be hosted on a secure server with the infrastructure, configuration and licenses that are consistent with current norms and laws to ensure safe and secure data storage and processing. Data will be preserved for a period of 20 years.

12.2 Monitoring and Quality Assurance

This study will be monitored by the CRU.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/principal investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The principal investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last postoperative outpatient visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study

report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

After the study is finished and analysed the trial management group will disclose the outcomes via presentation on international conferences and try to publish the results in an international medical Journal, whether the outcome is as expected or not.

Authorships will be based on the International Committee of Medical Journal Editors (ICMJE) guidelines. Key authors are AS and LW as first and second author, GvT, MB, and CvE shared senior author. Those who have participated in the conduct of the trial, and/or have included patients, are potential coauthors. Other contributors will be listed as collaborator.

13. STRUCTURED RISK ANALYSIS

Not applicable

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

d. Selectivity of the mechanism to target tissue in animals and/or human beings

e. Analysis of potential effect

f. Pharmacokinetic consideration

g. Study population

h. Interaction with other products

i. Predictability of effect

j. Can effects be managed?

13.2 Synthesis

Frequent supervision of participants as already had been done standardly.

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