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NEOPA: Sequential NEOadjuvant chemoradiotherapy (CRT) followed by curative surgery vs. primary surgery alone for resectable, non-metastasized Pancreatic Adenocarcinoma

Submission date	Recruitment status	[_] Prospectively registered
02/01/2014	No longer recruiting	[X] Protocol
Registration date	Overall study status	[_] Statistical analysis plan
11/02/2014	Completed	[X] Results
Last Edited	Condition category	[_] Individual participant data
20/05/2022	Cancer	

Plain English summary of protocol

Background and study aims
We are carrying out a study in people with pancreatic cancer in the head of the pancreas in which the tumour can be surgically removed. This study is comparing an intervention consisting of a preoperative combined chemoradiotherapy (CRT) and surgery with surgery alone without pre-treatment.
Our goal is to prove the effectiveness of the combined pre-treatment and surgery over surgery alone. The results of the study have the potential to considerably change the treatment regimen of patients with pancreatic cancer and help improve their treatment.

Who can participate?
Men and women over 17 years of age diagnosed with pancreatic cancer.

What does the study involve?
Patients are randomly allocated to either receive chemoradiotherapy (CRT) followed by surgical resection or receive surgery alone without any treatment before the surgery. Patients allocated to undergo CRT will receive Gemcitabine for 6 weeks combined with radiotherapy followed by surgical resection. Patients allocated to the reference group undergo primary surgery in curative intent. Irrespective of whether or not CRT has been
performed, all patients undergo adjuvant chemotherapy, preferentially with Gemcitabine.

What are the possible benefits and risks of participating?
All patients will receive an established treatment for pancreatic cancer in the head of the pancreas. Expected effects of the chemoradiotherapy treatment before surgery are a prolongation of 3-year survival and time to tumour recurrence, a higher rate of complete surgical resection and fewer postoperative complications. Potential risks of the CRT are a reduction of white blood cell count, which reduces the immune defence, resulting in infections,

and reduction of red blood cells and blood platelets. Other side effects are nausea, vomiting, diarrhoea, flu symptoms, respiratory problems, liver function disorders, allergic reactions and dysfunction of the kidneys.

Where is the study run from?
The organizing trial centre is the Department of General, Visceral and Thoracic Surgery at the University Hospital Hamburg, Eppendorf, Germany. Over 15 study centres across Germany are participating.

When is the study starting and how long is it expected to run for?
The study started in January 2014 and will run for a minimum of 6 years (3 years recruiting, 3 years follow-up).

Who is funding the study?
The study is funded by the Bundesministerium für Bildung und Forschung der Bundesrepublik Deutschland (Federal Ministry of Education and Research of the Federal Republic of Germany).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2012-003669-17

IRAS number

ClinicalTrials.gov number
NCT01900327

Secondary identifying numbers
N/A

Study information

Scientific Title
Sequential NEOadjuvant chemoradiotherapy (CRT) followed by curative surgery vs. primary surgery alone for resectable, non-metastasized Pancreatic Adenocarcinoma: NEOPA- a randomized multicenter phase III study

Acronym
NEOPA

Study objectives
Efficacy of neoadjuvant CRT in improving 3-year survival probability from 30% in the control arm undergoing upfront surgery without neoadjuvant CRT to 42% (relative increase of 40%) in the study arm undergoing CRT. The underlying guess of a 30% 3-year survival probability in the control group derives from an assumed median overall survival (MOS) of 20.7 months which corresponds with a MOS of 17.9 months to 23.6 months reported in several randomized trials.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee, Medical Association of Hamburg (Ethik-Kommission der Ärztekammer Hamburg), 17/12/2013, ref: PVN4472

Study design
Randomized multicenter phase III study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Biopsy-proven, non-metastasized, adenocarcinoma of the pancreatic head/uncinate process larger than 2 cm in size (≥cT2) and/or in close contact with the mesenterico-portal axis and superior mesenteric artery (SMA) (less than 3 mm).

Interventions

Group 1: Experimental intervention: Neoadjuvant CRT with weekly Gemcitabine 300 mg/m2 for 6 weeks combined with external beam radiotherapy (EBRT) delivering a total dose of 50.4 Gy over 28 days in 1.8 Gy fractions will be followed by classical or pylorus-preserving partial pancreato-duodenectomy (PD) and adjuvant chemotherapy (CTx), preferentially using Gemcitabine (1000 mg/m2, six cycles at day 1, 8, 15 of each 28-day cycle).

Group 2: Control intervention: Upfront PD followed by adjuvant CTx, preferentially with Gemcitabine (1000 mg/m2, six cycles at day 1, 8, 15 of each 28-day cycle).

Follow-up per patient: 36 to 72 months, depending on day of recruitment.

Duration of intervention per patient: 5 weeks CRT preceding surgery, which is scheduled 3 to 6 weeks after completion of CRT.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Survival time (3-year survival)

Secondary outcome measures
1. Histology-proven R0 resection rate based on a standardized histopathological handling of the surgical specimen.
2. Frequency of moderate and severe toxicity events and drop-out rate due to therapy-related toxicity (NCI Common Toxicity Criteria v2.0)
3. Resectability rate (Note: includes both R0 and R1 resection status)
4. Rate of unexpected intraoperative irregularities, operative time, blood transfusion requirement, postoperative morbidity rate, especially that of pancreatic fistula, and mortality rate
5. Rate of patients with severe postoperative complications (postop. recovery > 8 weeks) rendering adjuvant treatment worthless
6. Disease progression during neoadjuvant therapy
7. Quality of life analysis before neoadjuvant, before and 3, 6, 9, 12, 15, 18, 24, 30 and 36 months after surgery (EORTC QLQ C30 questionnaire)
8. Median disease-free survival (DFS, local and distant), overall survival (OS)
9. First site of tumor recurrence

Overall study start date
17/01/2014

Completion date
16/01/2020

Eligibility

Key inclusion criteria
1. Male and female, age 18 years and older
2. Histology-proven, resectable adenocarcinoma of the pancreatic head/uncinate process with a

tumor size greater than 2 cm (≥cT2) and/or close contact to the superior mesenteric vessels (≤3 mm in preoperative staging).
3. No evidence of metastasis to distant organs (liver, peritoneum, lung, others).
4. Serum creatinine level ≤ 3.0 mg/dl
5. Serum total bilirubin level ≤ 3.0 mg/dl in the absence of biliary obstruction. In the event of biliary obstruction, patients allocated to the CRT group must undergo interventional endoscopy or percutaneous drainage for biliary decompression. Post-interventionally, bilirubin levels should be ≤ 3.0 mg/dl before patients are subjected to CRT. In control patients undergoing upfront surgery, serum total bilirubin levels ≤ 10.0 mg/dl are tolerated, unless there are clinical and laboratory signs of severe cholangitis. Patients with serum total bilirubin level > 10.0 mg/dl undergo preoperative biliary decompression, preferentially by interventional endoscopy)
6. White blood cell count ≥ 3.5 x 109/ml, platelet count ≥ 100 x 109/ml
7. Ability to understand and willingness to consent to formal requirements for study participation
8. Written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
410

Key exclusion criteria
1. Age ≤ 18 years
2. Recurrent disease
3. Infiltration of extrapancreatic organs (except duodenum and transverse colon)
4. Persistent cholestasis/cholangitis despite adequate biliary stenting
5. Gastric outlet obstruction, especially in the event of endoscopically evidenced tumor invasion into the gastroduodenal mucosa.
6. Tumor-specific pre-treatment
7. History of gastrointestinal perforation, e.g. perforated colonic diverticulitis, abdominal abscess or intestinal fistula within 6 months prior to potential study participation
8. Radiographic evidence of severe portal hypertension/cavernomatous transformation that may, at the discretion of the participating investigators, hamper surgery
9. Other concurrent malignancies except for basal cell cancer of the skin and in-situ cervical cancer, premalignant hematologic disorders, e.g. myelodysplastic syndrome
10. Severe organ dysfunctions (e.g., liver cirrhosis ≥ Child B; Cardio-pulmonal diseases (NYHA ≥III, arrhythmia Lown III/IV, global respiratory insufficiency); ascites; acute pancreatitis; bleeding diathesis, coagulopathy, need for full-dose anticoagulation or INR > 1.5; other severe diseases that might prevent completion of the treatment regimen)
11. Chronic infectious diseases, especially immune deficiency syndromes, e.g. HIV infection, active tuberculosis within 12 months prior to potential study participation

12. History of severe neurologic disorders, e.g. cerebrovascular ischemia
13. History of prior deep venous thrombosis or pulmonary embolism
14. Pregnant or nursing women are ineligible and patients of reproductive potential must agree to use an effective contraceptive method during participation in this trial and for 6 months following the trial
15. Serious medical, psychological, familial, sociological or geographical conditions or circumstances potentially hampering compliance with the study protocol and follow-up
16. Participation in other clinical trials during the last 6 months before allocation to trial

Date of first enrolment
17/01/2014

Date of final enrolment
16/01/2020

Locations

Countries of recruitment
Germany

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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/01zgy1s35

Funder(s)

Funder type
Government

Funder Name
Bundesministerium für Bildung und Forschung der Bundesrepublik Deutschland (Federal Ministry of Education and Research of the Federal Republic of Germany (Germany) ref: 01KG1208

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	07/06/2014	09/08/2019	Yes	No
Basic results		25/04/2021	20/05/2022	No	No