Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: a multicentre randomized phase III clinical trial

Published: 09-08-2012
Last updated: 28-04-2024

Primary objectiveTo investigate whether the addition of preoperative radiochemotherapy to the standard treatment, consisting of explorative laparotomy, pancraticoduodenectomy if possible, followed by adjuvant chemotherapy, improves the overall...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Exocrine pancreas conditions
Study type	Interventional

Summary

ID

NL-OMON45151

Source
ToetsingOnline

Brief title
PREOPANC

Condition

- Exocrine pancreas conditions
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Pancreatic cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: KWF

Intervention

Keyword: chemotherapy, pancreatic cancer, radiotherapy, surgery

Outcome measures

Primary outcome

Primary endpoint

Overall survival is defined as the period of time between randomization and death from any cause. Patients alive at last follow-up are censored.

Secondary outcome

Secondary endpoints that will be compared between the randomization arms are defined as follows:

- Resection rate is defined as the percentage of eligible randomized patients that actually underwent a resection. Patients that do not undergo an explorative laparotomy at all or do undergo an explorative laparotomy but not a resection are considered a failure.
- R0 resection rate is defined as the percentage of eligible randomized patients that underwent a microscopically complete (or R0) resection. The resection is considered R0 if the inked margin is further than 1 mm distinct from any tumour cells.
- Disease free survival is defined as survival without overt recurrent

pancreatic cancer from the date of randomization, as discovered following complaints of the patient or on routine CT-scan at 6 months intervals. Any sign of recurrent or persistent disease, locoregional or distant, as well as death from any cause is considered an event for this endpoint. Patients that do not undergo an explorative laparotomy at all or do undergo an explorative laparotomy but not a resection are considered a failure at time point zero.
- Time to locoregional failure is defined as the period of time without locoregional recurrence after randomisation. Locoregional recurrence is considered an event and patients are censored at death or distant metastases without locoregional recurrence. Patients that do not undergo an explorative laparotomy at all or do undergo an explorative laparotomy but not a resection are considered a failure at time point zero.
- Time to distant metastases is defined as the period of time without distant metastases after randomisation. Distant metastases are considered an event and patients are censored at death.
- Postoperative complications are defined according to the internationally-accepted Clavien-Dindo classification and definitions of post-pancreatic surgery complications (pancreatic fistula, delayed gastric emptying, bleeding) by the International Study Group on Pancreatic Surgery (analysis on intent-to-treat and per-protocol in patients undergoing PD/Whipple).

Study description

Background summary

Pancreatic cancer has a dismal prognosis. Pancreaticoduodenectomy may offer cure but only a small percentage of patients can undergo a resection, and also in this cohort the survival is poor. Adjuvant chemotherapy offers a modest survival benefit. Based on multiple single-arm phase 2 studies and a SEER database observational study, it is suggested that preoperative radiochemotherapy may offer a survival benefit for patients with borderline resectable and resectable pancreatic cancer by increasing the resection rate and the R0 resection rate. The interpretation of these data is hampered by the lack of a control arm and the inherent selection bias of phase 2 studies (for example by only reporting on the subset of patients in whom a R0 resection is achieved). The only way to evaluate the role of preoperative radiochemotherapy concerning resection rate, R0 resection rate and subsequent overall survival is to perform a prospective randomized study with intent-to-treat analysis. To evaluate the benefit of preoperative radiochemotherapy the Dutch Pancreatic Cancer Group (DPCG) initiates a prospective randomized phase 3 study: PREOPANC. In this study, patients with borderline resectable and resectable pancreatic cancer are randomized between surgery followed by 6 months adjuvant chemotherapy with gemcitabine (the current standard), and neoadjuvant chemotherapy with 3 months gemcitabine to which radiotherapy is added in the 2nd month, followed by surgery and adjuvant chemotherapy with 4 months of gemcitabine (experimental arm). The feasibility of this schedule has been demonstrated in previous phase II studies. Resectability or borderline resectability will be assessed according to well-defined criteria. In the experimental arm, biliary drainage and laparoscopy will be performed before the start of radiochemotherapy. A total of 244 patients (176 events) are required to demonstrate a difference of 6 months (from 11 to 17 months) in median overall survival by intent-to-treat.

Study objective

Primary objective
To investigate whether the addition of preoperative radiochemotherapy to the standard treatment, consisting of explorative laparotomy, pancraticoduodenectomy if possible, followed by adjuvant chemotherapy, improves the overall survival (analyzed by intent to treat) of patients with resectable or borderline resectable pancreatic cancer.

Study design

Study design

This study is a multicenter, randomized, parallel superiority phase III clinical trial. Patients will be randomized between standard treatment or standard treatment preceded by laparoscopy and radiochemotherapy. Primary

outcome will be all-cause survival after randomization. All patients will be followed until death or at least 24 months after inclusion.
The survival data will be used for the evaluation of the survival difference between the two randomization groups. Randomization will be stratified for participating institution. Furthermore patients will be stratified to resectability/borderline resectability.

Intervention

Laparoscopy
In the radiochemotherapy arm, a laparoscopy will be planned so that the start of radiochemotherapy will not be later than 4 weeks after randomization. Laparoscopy is performed according to institutional guidelines. The minimum requirements of a successful procedure are: visualisation of the peritoneum, liver surface, diaphragm and base of the large bowel mesenterium. No peritoneal washings are performed. .

Chemoradiotherapy
In patients randomized to radiochemotherapy, if laparoscopy has not revealed peritoneal or liver metastases, radiotherapy to the pancreatic tumour with a margin for position variation and movement of the pancreas and tumour will be planned. A hypofractionated scheme of 15 fractions of 2.4 Gy in three weeks will be applied, combined with the second course of gemcitabine (gemcitabine 1000 mg/m2, day 1,8,15).

Study burden and risks

Side effects of the chemoradiation therapy as described in the protocol and in the patient information

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histologically or cytologically confirmed adenocarcinoma of the pancreas;2. Primarilly resectable tumours or Borderline resectable tumours ;3. Karnofsky performance status >= 70%;4. Ability to undergo surgery and radiochemotherapy;5. Leucocytes >= 3.5 X 10.9/l;6. Platelets >= 100X 10.9/l;7. Hemoglobin >= 6 mmol/l;8. renal function: E-GFR > 50 ml/min;9. Age >= 18 jaar;10.Written informed concent;11. Patients with reproductive potential must use effective contraception

Exclusion criteria

1.T1 resectable tumours, centrally located with no connection to the SMA, Celiac axis, CHA or SMV/PV;2. Clearly locally advanced, irresectable, tumours ;3. Carcinoma of the Papilla Vateri;4. Co morbidity precluding surgery or radiochemotherapy;5. Distant metastases, including cytologically proven N2 lymph node metastases (base of the celiac trunk or between inferior vena cava and aorta);6. Previous radiotherapy or chemotherapy precluding radiochemotherapy;7. Previous active malignancy shorter than 5 years before diagnosis of pancreatic cancer;8. Pregnancy;9. Imminent bowel obstruction;10. Active bleeding;11 Uncontrolled infection;12. Anamnestically known positive status for HIV or hepatitis B or C

Study design

Design

Study phase: 3

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-04-2013
Enrollment:	244
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	gemcitabine
Generic name:	Gemzar
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-08-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	11-12-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	01-11-2013
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-003181-40-NL
CCMO	NL40472.078.12