The role of the tumor microenvironment of pancreatic cancer to predict treatment outcome

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON44790

Source
ToetsingOnline

Brief title
Microenvironment of pancreatic cancer (MIPA)

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
pancreatic cancer; pancreatic tumor

Research involving
Human

Sponsors and support

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

Intervention

Keyword: hypoxia, pancreatic cancer, stroma, vasculature

Outcome measures

Primary outcome

For each imaging modalities one parameter will be regarded as primary study endpoint. For DWI the mean ADC of the whole tumor will be taken as primary study endpoint. From the different parameters that can be calculated from DCE-MRI, following the recommendations of the Pharmacodynamic/Pharmacokinetic Technologies Advisory Committee, Drug Development Office, Cancer Research UK, we will use mean Ktrans of whole tumor as primary study endpoint. For T2* the average value of the whole tumor will be taken. For 18F-HX4-PET/CT mean SUV of the whole tumor will be used as primary study end point. For the immunohistochemical analyses marker expression will be assessed in terms of stained surface area relative to the total tumor area.

Secondary outcome

For MRI, as mean values may average out differences and, therefore, underestimate differences in tumor physiology, exploratory histogram analyses will be performed. For 18F-HX4-PET/CT SUVmax will be determined as an exploratory endpoint.

Study description

Background summary

Pancreatic cancer is a highly lethal disease. Patients with resectable or borderline resectable disease may benefit from preoperative radiochemotherapy.

However, only a subset of patients will respond to this potentially toxic and expensive treatment. Therefore, novel predictive markers are needed to determine treatment efficacy at an early stage. Preferably, these markers could be determined non-invasively and provide insight into the biology of pancreatic cancer.

Pancreatic cancers are heterogeneous tumors. The tumor microenvironment is often characterized by large amounts of stroma, hypovascularization, and hypoxia. As these three factors can all contribute to treatment resistance, a quantitative assessment of these markers may aid in the prediction of response to preoperative radiochemotherapy. Moreover, these assessments may have prognostic value. Finally, further insight into the interrelation of these aspects of the tumor microenvironment can contribute to the evaluation of new targeted treatment options.

Tumor cellularity and extracellular matrix composition can be assessed non-invasively in vivo by diffusion weighted magnetic resonance imaging (DWI) and tumor vascularity can be assessed by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI). Finally, tumor hypoxia can be evaluated by T2* MRI and PET-CT, using the 18F-labeled hypoxic marker HX4.

Study objective

The primary aim of the study is to assess whether DWI, DCE-MRI, T2*, and 18F-HX4-PET/CT predict overall survival in patients with pancreatic cancer treated with surgery and adjuvant chemotherapy or with neoadjuvant radiochemotherapy, surgery and adjuvant chemotherapy. Secondary aims of the study include the assessment of the predictive value of DWI, DCE-MRI, T2*, and 18F-HX4-PET/CT for pathological response to neoadjuvant chemoradiation, the correlation of DWI, DCE-MRI, T2*, and 18F-HX4-PET/CT with histopathological assessment of tumor stroma, vascularization, and hypoxia, and the assessment of the predictive value of these histopathological markers for overall survival.

Study design

The target population will be recruited from the the Acdemic Medical Centre (AMC) and Erasmus MC. First, to assess reproducibility, patients with pancreatic cancer will undergo MRI twice, once in the AMC and once in the EMC. Next, 40 consecutive patients that will undergo surgery+adjuvant treatment will have MRI and 18F-HX4-PET/CT measurements once to assess the value of the techniques to predict outcome of standard treatment. 40 patients who will undergo preoperative radiochemotherapy will have MRI and 18F-HX4-PET/CT at baseline, and 1 week before surgery. We will assess the relative contribution of each imaging method as well as the integrated use of these methods as predictive markers for survival and pathological response to treatment. Tumor tissue from resected patients will be analyzed for markers of tumor

vascularization (CD31, VEGF), hypoxia (HIF1alfa, GLUT1, CA9), and stromal activation (smooth muscle actin, markers for Hedgehog pathway activity). Results will be correlated with imaging parameters, as well as patient outcome.

Study burden and risks

* The patient will not have a direct benefit from the study.
* The administration of Gadolinium involves a very small risk of an acute allergic reaction.
* The administration of Buscopan involves a risk of an adverse reaction. The most common adverse reactions are accommodation disorders, tachycardia, vertigo and a dry mouth. Patients who have a contraindication for IV administration of Buscopan (mega-colon, ileus, myasthenia gravis, glaucoma, prostate hypertrophy with urine retention, intestinal stenosis and tachycardia), will undergo the scans without administration of Buscopan.
* The proposed 18F-HX4 dose is chosen based on the phase 1 study with 18F-HX4.75 In this study no toxicities were observed except for a mild, grade I headache one day after 18F-HX4 injection, which was considered unlikely to be related to the injection. In view of previous experiences with 18F-HX4, conventional PET-CT and other nitroimidazole drugs, we expect no side effects. Nevertheless, it cannot be excluded that patients will experience an acute allergic reaction to 18F-HX4. Therefore, all patients will be monitored carefully during and directly after administration of the labelled 18F-HX4 by trained caregivers.
* Participation in the study will involve exposure to radiation that is estimated to be 16.4 mSV for the maximum of two 18F-HX4-PET/CT scans together. The theoretical chance for radiation-induced cancer induction is 5% per Sievert. For a radiation exposure of 10 mSv this implies a chance of 1 in 2000. This number applies to patients of 30 years of age. The risk reduces with ~50% for a typical oncological population of patients aged 55-70 years. Moreover, a substantial portion of patients will be treated with radiotherapy. Radiation exposure due to the 18F-HX4 scans is negligible compared to radiation exposure because of the clinically delivered radiotherapy.
* Whenever possible, MRI and 18F-HX4-PET/CT scans will be performed on one day. Nevertheless, this will most probably involve an extra visit to the hospital for most patients. Also, patients participating in the reproducibility part of the study and patients treated with chemoradiation will undergo MRI and 18F-HX4-PET/CT scanning twice and, therefore, will have to come to the hospital twice.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Patients with pancreatic tumors, with histological or cytological proof of adenocarcinoma or a high suspicion on CT imaging.
* Tumor size * 1cm.
* WHO-performance score 0-2.
* Scheduled for surgery or neo-adjuvant chemotherapy/radiation followed by surgery. For the reproducibility part of the study, patients who will not undergo surgery, may be included, too.
* Written informed consent.

Exclusion criteria

* Any psychological, familial, sociological or geographical condition potentially hampering adequate informed consent or compliance with the study protocol.
* Contra-indications for MR scanning, including patients with a pacemaker, cochlear implant or neurostimulator; patients with non-MR compatible metallic implants in their eye, spine, thorax or abdomen; or a non-MR compatible aneurysm clip in their brain; patients with severe claustrophobia.
* Renal failure (GFR < 30 ml/min) hampering safe administration of Gadolinium containing

MR contrast agent.
* For the reproducibility part of the protocol: surgery, radiation and/or chemotherapy foreseen within the timeframe needed for MR scanning.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-11-2013
Enrollment:	95
Type:	Actual

Ethics review

Approved WMO Date:	28-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	23-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL45913.018.13