CROSSFIRE trial: Crossatlantic Randomized controlled trial comparing Outcome in Survival after Systemic plus Focal therapy for Inoperable pancreatic carcinoma: Radiotherapy versus irreversible Electroporation

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The objective of this study is to compare the efficacy of chemotherapy and IRE (experimental arm) to the efficacy of chemotherapy and radiation (control arm) in patients with locally advanced, non-resectable, non-metastasized, pancreatic cancer.

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

Summary

ID

NL-OMON50215

Source
ToetsingOnline

Brief title
Treatment efficacy of SABR compared with IRE for LAPC

Condition

- Exocrine pancreas conditions
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Locally advanced pancreatic carcinoma, synonyme: inoperable pancreatic cancer without metastases

Research involving
Human

Sponsors and support

Primary sponsor: Radiologie & Nucleaire Geneeskunde
Source(s) of monetary or material Support: Ministerie van OC&W,Addessium,AngioDynamics

Intervention

Keyword: Irreversible electroporation (IRE), Locally advanced pancreatic carcinoma (LAPC), Nanoknife, Stereotactic ablative radiotherapy (SABR)

Outcome measures

Primary outcome

The primary outcome of the study is efficacy in terms of overall survival.

Secondary outcome

Secondary outcomes are progression free survival, safety/toxicity,

immunomodulation, tumor marker CA-19.9, quality of life, and total direct and

indirect costs for each treatment arm (cost-effectiveness analysis).

Study description

Background summary

Pancreatic adenocarcinoma is one of the most aggressive forms of cancer, for which survival hardly improved over the past 40 years. It is the 4th leading cause of cancer-related death in Europe and the United States. Pancreatic cancer has the highest mortality rate of all major cancers; 94% of pancreatic cancer patients will die within five years of diagnosis, 74% within the first year of diagnosis; only 6% will survive for more than five years. Surgical resection is the only curative option. However, about 40% present with non-metastatic locally advanced pancreatic carcinoma (LAPC; AJCC stage III). These patients are not eligible for surgical resection because the tumor involves major blood vessels such as the superior mesenteric artery, celiac axis, common hepatic artery and/or portal vein. These patients are currently treated with palliative chemotherapy as first line therapy. Focal therapy using

external beam radiation therapy (EBRT) may further improve survival, but outcome remains poor. Stereotactic ablative radiotherapy (SABR) is a form of EBRT that has important advantages over conventional radiotherapy such as a more precise and greater biological dose delivery and hence less toxicity and presumably better outcome.
For patients diagnosed with LAPC, a combination of chemotherapy plus local tumor destruction using irreversible electroporation (IRE), a novel tumor ablation technique, has recently shown great promise. IRE is based on permeabilization of the cell membrane through electrical pulses leading to apoptosis. Theoretically, IRE only affects viable tumor tissue, leaving surrounding vital structures relatively intact. It is therefore considered to cause less morbidity than thermal ablative strategies. Several studies have investigated the safety and efficacy of IRE for LAPC. However, up until now no randomized controlled trial has been conducted.
Although for now the primary aim remains macroscopically complete tumor destruction, preliminary data, obtained at the VUmc immuno-oncology research institute in Amsterdam, suggests the induction of a T-cell mediated systemic immune response. This may represent a so-called *abscopal effect*, referring to the phenomenon where localized treatment of the primary tumor induces a forceful immune response, targeting occult distant micrometastases which could have an additional positive effect on recurrence-free and overall survival.

Study objective

The objective of this study is to compare the efficacy of chemotherapy and IRE (experimental arm) to the efficacy of chemotherapy and radiation (control arm) in patients with locally advanced, non-resectable, non-metastasized, pancreatic cancer.

Study design

Amsterdam UMC, location VU University Medical Center and location AMC (Amsterdam, the Netherlands), Radboud University Medical Center (Nijmegen, The Netherlands) and the Miami Miller School of Medicine (Miami, Florida, USA) will participate in this phase II/III study to define the efficacy of systemic chemotherapy followed by IRE versus systemic chemotherapy followed by SABR. All patients with radiologically and histopathologically proven LAPC <5 cm in largest diameter will be discussed at the weekly multidisciplinary meeting. If they meet the inclusion criteria and formally consent, they will be randomized into one of the two arms. Patients in both arms will receive 4 cycles of FOLFIRINOX followed by either percutaneous CT-guided IRE (experimental arm, n = 69) or SABR (control arm, n = 69). After patient recovery (>6 weeks post-procedure), FOLFIRINOX will be continued. To examine the immunologic response before and after SABR and IRE, venous blood sampling will be performed.

AMENDMENT (14-05-2020):

The CROSSFIRE-study is a single center, randomised, prospective phase II/III efficacy study. Participating hospital is the Amsterdam UMC, location VUmc.

Intervention

Irreversible electroporation (IRE) is a novel image-guided tumor ablation technique in which the mechanism of cell destruction is primarily based on a non-thermal effect. The application of multiple short high-voltage electrical pulses leads to the formation of microscopic perforations of the cellular membrane of 100-150 nanometer. As a result, the cells lose their homeostatic capabilities and will go into the process of apoptosis. The * mostly theoretic - advantage over other local ablative techniques is that IRE selectively destroys all cells within the ablation zone, whilst the extracellular matrix structures remains intact. As a result, the anatomical framework to which vulnerable structures such as bile ducts, blood vessels, ureters and nerves derive their strength, is presumed to remain intact during IRE. For this reason, tumors in the proximity of these critical structures can be ablated safely. Although long-term follow-up results are still unknown, the future of IRE for the minimally-invasive destruction of difficult-to-reach tumors, seems promising.

Study burden and risks

A recent advancement in radiation therapy is SABR delivering higher doses of radiation per treatment fraction more precisely to the tumor. Visualization of the pancreatic tumour and its surrounding normal organs prior to and during radiation delivery can be used to deliver *gated* treatment (beam-on only when the tumour is in the predetermined position) using small uncertainty margins and thereby limiting the dose delivered to normal organs, likely resulting in decreased toxicity. Disadvantages for patients include the need to be positioned within the MRI bore during radiation delivery, and a prolonged time per treatment fraction (estimated at 30-60 minutes per fraction), which has to be weighed against the use of a total of only five fractions.
Several studies have investigated the safety and efficacy of open and percutaneous IRE for locally advanced disease, with an overall complication rate of 10-37% and an overall survival time from IRE ranging from 16.0 to 24.9 months. One trial compared the results to a matched group of patients treated with chemoradiation alone which showed a potential survival benefit of 9 months in favor of the IRE group. Clinically relevant complications are expected in up to 17% of procedures with a 1-2% mortality rate.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Screening must be performed no longer than 2 weeks prior to study enrollment.
Subjects are eligible if they meet the following criteria:
* Radiologic confirmation of LAPC by at least ceCT of chest and abdomen (with the upper abdomen scanned according to a dedicated 3mm slice multiphase pancreatic tumor protocol);
* Maximum tumor diameter * 5 cm;
* Histological or cytological confirmation of pancreatic adenocarcinoma;
* Age > 18 years;
* World Health Organisation scale (WHO) performance status 0 * 1 ;
* Adequate bile drainage in case of biliary obstruction;
* Written informed consent;

Exclusion criteria

Subjects who meet the following criteria at the time of screening will be

excluded:, - Resectable pancreatic adenocarcinoma as discussed by our multidisciplinary hepatobiliary team;
- Stage IV pancreatic carcinoma;
- Trans-mucosal tumor invasion into surrounding duodenum or stomach;
- History of epilepsy;
- History of cardiac disease: Congestive heart failure >NYHA class 2, Active Coronary Artery Disease (defined as myocardial infarction within 6 months prior to screening), Ventricular cardiac arrhythmias requiring anti-arrhythmic therapy or pacemaker (beta blockers for antihypertensive regimen are permitted; atrial fibrillation is not contra-indicated);
- Uncontrolled hypertension;
- Compromised liver function (e.g. signs of portal hypertension, INR > 1,5 without use of anticoagulants, ascites);
- Uncontrolled infections (> grade 2 NCI-CTC version 3.0);
- Pregnant or breast-feeding subjects.
- Immunotherapy prior to the procedure;
- Radiotherapy prior to study enrollment;
- Any implanted stimulation device;
- Any condition that is unstable or that could jeopardize the safety of the subject and their compliance in the study;
- Contra-indications for MRI

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2016
Enrollment:	75

Type:	Actual

Medical products/devices used

Generic name:	Irreversible electroporation (IRE); interventional radiology
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	12-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2020
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

ID: 22388
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
ClinicalTrials.gov	NCT01939665
CCMO	NL55158.029.15
OMON	NL-OMON22388