Metabolic Imaging to Improve Patient-Specific Therapy Outcome

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Primary objective • In this study we will investigate whether biochemical imaging of change (Δ, figure 1) in the metabolic phospholipid ratios of PME and PDE between baseline and after 2 weeks of therapy are predictive for progression free...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational non invasive

Summary

ID

NL-OMON55904

Source
ToetsingOnline

Brief title
MAESTRO

Condition

- Hepatic and hepatobiliary disorders

Synonym
metastatic colon cancer, metastatic gastro-oesophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO,Merck,Servier

Intervention

Keyword: High field MRI, Metabolic Imaging, Spectroscopy, Therapy response

Outcome measures

Primary outcome

The main study parameters include the metabolic ratio of the phospholipids PME and PDE from the area under the curve (AUC) of the corresponding spectral peaks. Metabolites are identified and quantified in the spectra using LCModel and AMARES. Partial least squares discriminant analysis and linear mixed models are used to identify significantly altered phospholipid metabolism. The main endpoint is defined by the RECIST progression criteria after every nine weeks assessed using tumour size measurements from standard-of-care CT scans together with the overall survival.

Secondary outcome

The secondary study parameters and endpoints include the response to treatment following the RECIST progression criteria, progression free survival, overall survival, ratios of other MR detectable metabolites from multiple nuclei and their individual metabolite changes.

Study description

Background summary

Non-communicable diseases are the cause of a majority of the global death, with cancer expected to rank as leading cause in the upcoming years. The incidence of gastrointestinal cancers is largely attributing to the global increased cancer incidence, with colon cancer ranking as the fourth most common site of newly diagnosed cancer in 2018 (colon cancer (6.1%), oesophageal cancer (3.2%) and pancreatic cancer (2.5%))[1]. In 2018, gastrointestinal cancers made-up

15.5% of all global cancer related deaths in 2018. Although treatment strategies have improved, patients suffering from metastasized gastrointestinal cancer often receive ineffective treatments or undergo periods of therapy resistance because tumor non-response is hard to detect, especially in early stages of therapy. For example, 50% of patients will experience progression within six cycles (54 weeks) of first line treatment [2]. One of the reasons is that, currently, the primary ineffectiveness of a treatment cannot be determined earlier than nine weeks by assessment of morphological changes via RECIST following start of therapy [3,4].

Metabolomics studies body functions through the measurement of metabolites, chemical signatures of cellular processes. The capacity of metabolomics to identify specific pathways to characterize tissues has been demonstrated by recent studies [5], not only via cultured organoids from biopsies [6], but also intra-operatively via a mass-spectrometry pen [7], demonstrating 96% accuracy. MRI (Magnetic Resonance Imaging), is able to provide 3D images of the body. In conventional MRI the resonance of only hydrogen nuclei (1H) are registered. Therefore, MRI is often limited to morphological imaging, essentially mapping water and fat, providing little information on chemical composition and biological processes [8]. Initial studies focusing on a single nucleus to examine biological processes have shown potential (e.g., brain scans), but additional research is required to develop a chemical imaging technology for the full human body and to include a broad spectrum of nuclei such as phosphorus (31P) and sodium (23Na) but also deuterium (2H), fluorine(19F), oxygen (1O) and carbon (13C) [9-11]. Technological breakthroughs in detecting all biologically relevant nuclei opened up the possibility to provide dynamic 3D maps of metabolic and physiologic activity, which may be linked to clinical parameters, such as response to therapy [12-15]. Full body metabolic imaging with MR, however, is not yet clinically feasible as a result of the following challenges: i.) The RF wavelength of the proton (1H) imaging signals is much shorter (<=11 cm) than the dimensions of the human body (non-uniformities) [8]; ii.) Signals from metabolites are often obscured by other metabolites and highly abundant signals (e.g., water, lipids and surrounding tissues such as muscles) [9,16]; iii) Frequency shifts are caused by decreased B0-field homogeneity due to susceptibility differences of tissues or (non-magnetic) metals such as clips used in surgery; iv.) Many organs are moving due to respiration and pulsating blood flow, resulting in ghosting artefacts during relatively long metabolic scan sessions; v) The relatively low abundant X-nuclei require numerous high energetic RF pulses to regain signal, consequently increasing specific absorption rate (SAR) which limits the maximum imaging volume.

However, recent studies reported full organ coverage 31P MRSI at 7T is feasible in the liver, heart and lungs using a 31P whole body birdcage coil.[12,17-19] This hardware improvement allows fast 31P MRSI over large volumes of interest without a necessary increase in SAR. The frequencies of 31P (120.6Mhz) and 23Na (78.8Mhz) at 7T are lower than 1H and results in less destructive RF

interference due to the increased wavelengths, improving the 31P B1+-field homogeneity compared to conventional 1H 7T MRI or conventional 31P surface coils used only for local and surface MRS applications. In addition, the signals of all 31P metabolites are well separated due to the increased spectral resolution at 7T, improving the detection of individual metabolites without any necessary post-processing steps. However, signal contamination from neighbouring tissue is still present from high abundant signals such as surrounding muscles and need to be assessed and minimized using specific imaging and processing strategies [10,16] Inhomogeneity of the main magnetic field (B0) can be overcome using conventional shimming techniques, however, large volumes are difficult to shim, with increasing difficulty at higher field strengths. Current advances demonstrate the use of a local shim coil arrays which increases the degrees of freedom available to improve B0 field homogeneity [20,21]. The fast repetitions and large number of averages which result in a long scan protocol, make it impractical to perform breath-hold triggered MRSI. Strategies to correct for bulk motion induced artefacts use 1H navigator images or 31P navigator spectra, however, have not been explored in MR spectroscopic imaging.
Unlocking the potential of the available 7T MR technologies allows development of new methodologies to image a full scale of chemical processes in the human body, via the detection of a wide spectrum of relevant nuclei.

Phosphorus (31P) MRSI allows monitoring tissue metabolism by measuring specific energy-and phospholipid-metabolites. Phosphocreatine (PCr), Adenosine triphosphate (ATP, with α-, ß- and γ- resonances) and inorganic phosphate (Pi) give insight into cell energy metabolism and the ratios between these metabolites are already used as diagnostic indicators in systemic diseases [22-24]. Inorganic phosphate (Pi) can also serve as a diagnostic marker for tissue pH as its resonance frequency changes with the acidity of the environment and distinguish between extracellular and mitochondrial species [25]. In addition, 31P MRSI at 7T is able to detect cell membrane precursors, the phosphomonoester (PME) and cell membrane degradation products, the phosphodiesters (PDE). The increased SNR and increased spectral resolution at 7T allow discrimination of individual PME metabolites namely phosphocholine (PC) and phosphoethanolamine (PE), but also individual PDE metabolites glycerophosphocholine (GPC) and glycerophosphoethanolamine (GPE). Previous studies show alterations of PME to PDE ratios (PC to GPC, PE to GPE) suggest proliferation and are often found in tumor tissue [4, 11, 26-30]. Changes in these ratios during therapy are markers of therapy response and take place well before morphological changes can be observed [31-35].

However, to the best of our knowledge, up until now no clinical studies using whole body multinuclear MR spectroscopic imaging have been performed. In order to lay the foundation to the study of human biology using non-invasive chemistry imaging, unique nuclei at 7T and corresponding acquisition strategies for patient friendly scan times will be used. To demonstrate the feasibility of dynamic 3D whole body chemical imaging within patient* tolerable scan times and

its potential for early response monitoring and therapy prediction, MAESTRO will research a stratification strategy for patients with liver metastasis of gastro-oesophageal cancer receiving first line palliative chemotherapy and immunotherapy when applicable, in a 70 patient observational study.

With the MAESTRO approach, the consortium aims at reducing the 9-weeks period before therapy efficacy evaluation to less than three weeks (> 66% reduction). Moreover, MAESTRO aims to develop a new stratification strategy to dynamically differentiate between responders and non-responders two months earlier than current clinical standards by assessing differentiating biochemical markers by metabolic imaging throughout the first-line treatment course of individu

Study objective

Primary objective
• In this study we will investigate whether biochemical imaging of change (Δ, figure 1) in the metabolic phospholipid ratios of PME and PDE between baseline and after 2 weeks of therapy are predictive for progression free survival (PFS) and/or overall survival (OS) in gastro-oesophageal cancer patients within 27 weeks of treatment.

Secondary objectives:
• In this study we will investigate whether biochemical imaging of change (Δ, figure 1) in the metabolic phospholipid ratios of PME and PDE between baseline and after 2 weeks of therapy are predictive for RECIST progression in gastro-oesophageal cancer patients after the first 9 week treatment period.
• Investigate whether biochemical imaging of the metabolic phospholipid ratios of PME and PDE at baseline of therapy are predictive for RECIST progression after the first 9-week treatment period, and for PFS and OS in gastro-oesophageal cancer patients.
• Investigate whether biochemical imaging of change (δ, figure 1) in the metabolic phospholipid ratios of PME and PDE after a 9-week treatment period are predictive for RECIST progression following that treatment period, and for PFS and OS in gastro-oesophageal cancer patients.
• Exploratory multi variable analysis for the development of a prediction model to predict resistance to treatment within 3 weeks after the start of chemotherapy with the use of all chemistry imaging data including all MR detectable nuclei and clinical parameters.

Figure 1: C1 - research protocol, chapter 3; study design.

Study design

In this multi-centre observational cohort study, patients with liver metastasis of gastro-esophagogastric cancer will be asked for participation in the study. After eligible patients have signed informed consent, patients will continue to

receive standard treatment as scheduled. Standard CT-scans at baseline, t = 9 and 18 weeks will be supplemented with MAESTRO-scans. In addition, after the first chemotherapy cycle at t = 2 weeks, a MAESTRO-scan will be made to assess early response monitoring. Patients are followed until disease progression according to RECIST 1.1 progression criteria is detected by CT scan or until t = 27 weeks. The scan time of MAESTRO-scans will approximately be one hour.

To meet the primary objective the baseline and 2 weeks after start therapy chemical imaging measurements (Δ, figure 1) are used to predict the RECIST progression 27 weeks after the start of the treatment. In addition, solely the baseline measurement will be used to predict the RECIST progression, OS and PFS, after the 9-week treatment period to meet the secondary objectives. All other imaging moments every 9 weeks (δ, figure 1) of therapy are used to predict RECIST progression, OS and PFS following the 9-weeks period of treatment.

(NB. See chapter 3; study design of C1, the research protocol for figure 1.)

Study burden and risks

Patients will be asked for three extra hospital visits to undergo 7T MRI of approximately one hour per session (3 x 1 hour). MRI is a safe non-invasive technique without use of ionizing radiation and so far, extensive research has not shown any side-effects of the high magnetic field used in 7T MRI, resulting in low inherent risks for the participants. Patients' therapy is not delayed by participation in this study and patients with MRI contraindications are excluded from participation.

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• 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 claustrophobia; patients with an abdominal circumference which exceeds MRI-bore circumference.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Patients with liver metastasis of gastro-oesophageal cancer, with histological or cytological proof of
metastasis or a high suspicion on CT imaging whom are scheduled for first line palliative chemotherapy.

2. 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 claustrophobia; patient with an

abdominal circumference which exceeds MRI-bore circumference.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-07-2022
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	04-06-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

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Approved WMO Date:	12-03-2025
Application type:	Amendment
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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
ClinicalTrials.gov	NCT04534543
CCMO	NL72636.018.20