Technical validation of quantitative methods for 3 'deoxy-3-[18F] fluorothymidine ([18F] FLT) PET in liver metastases of colorectal cancer patients

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Ethical review	Approved WMO
Status	Completed
Health condition type	Metastases
Study type	Observational invasive

Summary

ID

NL-OMON41755

Source
ToetsingOnline

Brief title
FLT PET Liver

Condition

- Metastases

Synonym
Colorectal liver metastasis, metastasis of gut cancer in the liver

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: IMI QuIC ConCePT (EU project)

Intervention

Keyword: CRC, FLT, Liver, PET

Outcome measures

Primary outcome

The proportion of number of concordant lesion observed with both [18F] FLTPET

and CT scans on the total number of lesions observed with the CT scan

(qualitative assessment).

Secondary outcome

1. Measurements per lesion from full kinetic filtering model

2. Measurements per lesion from simplified models

3.Test-retest reproducibility of each quantitative assessment of tumor [18F]

FLT uptake

4. Correlation of full kinetic modeling with more simplified model per lesion

Study description

Background summary

Principle of positron emission tomography (PET)
PET is a non-invasive imaging technique based on the use of biologically relevant compounds labelled with short-lived positron-emitting radionuclides such as carbon-11, nitrogen-13, oxygen-15 and fluorine-18. In clinical applications, a very small amount of labelled compound (radiopharmaceutical or radiotracer) is introduced into the patient usually by intravenous injection and the concentration of tracer in tissue is measured using the scanner. During its decay process, the radionuclide emits a positron which, after travelling a short distance (1-2 mm), encounters an electron from the surrounding environment. The two particles combine and "annihilate" each other resulting in the emission in opposite directions of two γ-rays of 511 keV each. The image acquisition is based on the external detection in coincidence of the emitted γ-

rays, and a valid annihilation event requires a coincidence between two detectors on opposite sides of the scanner. For accepted coincidences, lines of response connecting the coincidence detectors are drawn through the object and used in the image reconstruction.

[18F]fluorothymidine (FLT): measuring tumor cell proliferation
The most widely used PET tracer, and the only one currently approved by the US Food and Drug Administration, is [18F] FDG (2-fluoro-2-deoxy-D-glucose), which canbe used in the diagnosis, staging, treatment monitoring and radiotherapy planning of a number of cancers. However, since FDG is not tumor specific and both false-positive and false- negative results are common, there is ongoing research into possible alternatives, including [18F] FLT [1]. [18F] FLT-PET is widely investigated as a proliferation marker in oncology. [18F] FLT follows the salvage pathway of endogenous thymidine in the cell. However, unlike thymidine, [18F] FLT is trapped in the cytosol and is not incorporated into DNA. This process supplements the pool of thymidine monophosphate provided by de novo synthesis. After intravenous injection, [18F] FLT enters tumor cells both via a nucleoside transporter and partly via passive diffusion. Inside proliferating cells, FLT is accepted as substrate by thymidine kinase 1 (TK-1), which phosphorylates it, thereby trapping it in cells.
FLT-monophosphate is further phosphorylated to di- and triphosphate forms. Phosphorylation by TK-1 is the rate limiting step in FLT accumulation in proliferating cells, causing FLT to accumulate in proportion to TK-1 activity [2]. Published data on [18F] FLT-PET are heterogeneous and it is not clear to what extent this relates to different pharmacokinetic characteristics, biological changes, image resolution, or quantification methods. To date, the majority of clinical research studies of FLT-PET in humans have focused on validating it as an accurate measurement of proliferation in a broad spectrum of cancers,
and assessing its usefulness for diagnosing and staging malignancies. However, FLT undergoes predominantly hepatic metabolism to form FLT-glucuronide and therefore shows high physiological uptake in the liver, with the result that tumors (metastases) in the liver can prove difficult to identify. The accurate detection of proliferation of liver tumors with FLT is therefore a clinically relevant problem. There are 2 approaches to image analysis with [18F] FLT PET. One simple method, which is practical in the clinic uses the standardized uptake value
(SUV) derived from static images. The second method uses dynamic image sequences and kinetic modeling of tracer uptake. Pharmacokinetic (pk) modelling of PET tracers is the gold standard but it requires arterial blood sampling and dynamic scanning. In case of [18F] FLT, the net uptake rate constant of [18F] FLT, Ki, determined by non-linear regression (NLR) of an irreversible two-tissue compartment model is typically used as the gold standard. Two simplified methods often are used to (semi-)quantitatively assess [18F] FLT uptake: graphical (Patlak) analysis [3] and standardized uptake values (SUV). Patlak analysis assumes irreversible trapping in tissue, and its accuracy thus depends on the assumption that no significant dephosphorylation occurs within

the time course of the study. Both NLR and Patlak measure net uptake of [18F] FLT, taking into account the concentration of tracer in plasma during the course of the study. Only NLR, however, allows for measurements of individual rate constants between compartments and for an implicit correction for blood volume in the tissue of interest. SUV is the ratio of tissue concentration and injected activity at a certain time after administration of the tracer. It does not take tracer kinetics into account, but has the advantage that it is a single scan procedure that does not require plasma data. In daily clinical practice, a static PET scan in whole body mode is the preferred clinical procedure. In this context only SUV is feasible. Alternatively, kinetic filtering methods have been proposed for the detection of liver tumors, requiring procedures of similar complexity [4]. This procedure is not suited for daily clinical practice and it is not suited for whole body acquisitions.

Detection of liver metastases with FLT-PET

Francis and coworkers reported imaging 17 patients with primary or CRCs, all 6 peritoneal metastases and 5 of 6 lung metastases. However, only 11 of 32 liver metastases were detected because of high background activity in the liver, caused by glucuronidation of FLT [5]. Zhou et al. investigated [18F] FLT PET/CT in pretreatment evaluation of metastatic gastric cancer and compared it to [18F] FDG PET/CT. In the liver and the bone marrow, sensitivity of FLT PET/CT versus FDG PET/CT for detecting liver metastases and bone metastases was 30% (6/20) versus 100% (20/20) and 1/5 (20%) versus 5/5 (100%), respectively ($P < 0.05$). This group concluded that FLT PET/CT imaging is not recommended for pretreatment assessment of metastatic gastric cancer as it is not competent enough to evaluate liver and bone metastases, moreover the high background hepatic uptake may also cover gastric primary tumors located adjacent to the liver. However, SUVmax were calculated for both radiotracers and no other filtering methods were applied [6]. Gray et al. enhanced visualization of tumors imaged with FLT-PET by using nonlinear kinetic filtering. A classification algorithm was developed to isolate cancerous tissue from healthy organs and was validated using 29
scans from patients with locally advanced or metastatic breast cancer. First, metastatic CRC using FLT-PET. FLT-PET successfully detected all 6 primary dose-normalized average time versus radioactivity curves for the major tissue types were generated, and each image voxel was then classified according to the tissue type it most likely to represent based on a comparison of its time profile with those of the predefined classes. Images of only voxels likely to show tumor tissue were then produced, by setting the intensities of all other voxels to zero. Success of the filter in removing signal from healthy tissue, whilst retaining that from tumor tissue, was assessed both qualitatively and quantitatively. Reliability was quantified using test-retest data. A large reduction in signal from the liver of 80% was observed following application of the kinetic filter, whilst the majority of signal from both primary tumors and metastases were retained. A scan acquisition of 60 minutes showed to be sufficient to obtain the necessary results [2].

Post therapy FLT-PET
For simplified uptake measures to be valid for monitoring response or predicting outcome, their relationship with the more accurate outcome measures of full kinetic analysis must be similar before and after therapy [7]. However, systemic therapy might alter the correlations between NLR, Patlak and SUV, as has previously

Study objective

To investigate lesion detection in patients with liver metastases of colorectal cancer with [18F] FLT-PET compared to CT at baseline (= gold standard). This investigation will be done based on a qualitative assessment of the scans ([18F] FLT-PET and CT).

Secondary objectives:
1. To correlate the kinetic model measurements and simplified measurements from the [18F] FLT PET
2. To determine test-retest reproducibility of quantitative assessment of liver metastases* [18F] FLT uptake
3. To achieve a clinically feasible protocol f.e for dynamic PET, scan durations < 30 minutes
4. To investigate change in FLT tumor uptake after two cycles of therapy and compare it against a radiological response (RECIST) as gold standard measured after 6 cycles of therapy

Study design

Prospective observational monocenter, multinational study on patients with mCRC (liver metastases > 20 mm in diameter) will be scanned with [18F] FLT-PET on 2-3 separate occasions. Double baseline assessments (testretest) of FLT-PET should be done within 1 week prior to first drug administration, and the interval of test-retest should be between 24 hours (decay of [18F]) to 7 days. During the therapy period, an optional third FLT PET scan could be performed at the end of the second cycle (f.e. after 4 weeks for Folfox therapy). A diagnostic CT will be performed together with the first and the third FLT PET scan. The dynamic PET scans centered over the liver will be performed on a PET-CT scanner. During PET, venous samples will be taken at different time points. Dedicated in-house developed software will be used to quantify kinetics. Personal and tumor characteristics will be registered (age, sex, body weight and height, co-medication). Patients will be recruited by the Antwerp University Hospital, Belgium (Prof. Dr. Stroobants S, Prof. Dr. Peeters M), VUmc, Amsterdam, The Netherlands (Prof. dr. Hoekstra O.S.), UMC St Radboud Nijmegen, The Netherlands (Prof. Dr. Oyen W), Manchester Cancer Research Centre, Manchester, UK (Prof. Dr. Jackson A).

Study burden and risks

A PET scan is a regular diagnostic imaging technique. Each study will be conducted in compliance with the radiation safety guidelines of the department. Based on results we obtained from biodistribution studies in rats, whole body radiation after intravenous injection of 300 MBq [18F] FLT is approximately 6.5 mSv, including the low dose CT used for attenuation correction. Since patients will undergo upto 3 FLT-PET scans, this will result in a radiation dose of 19.5 mSv for the experimental component of the study. In addition, the patient will undergo diagnostic CT scans as part of the standard of care (8-9 mSv per scan) To compare, every person living in Belgium receives a natural background radiation dose of 2.5 - 3 mSv per year. The maximum annual amount of radiation allowed for a radiation worker such as a CT technologist or radiologist, equals 20 mSv per year. The results of this study may have great clinical benefit in using [18F] FLT PET-CT as drug monitoring tool in the future, improving personalized therapy strategies for cancer patients. We therefore consider the additional radiation burden acceptable.

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

Patient age 18 years or older
Histological diagnosis of mCRC (stage IV) without options for localregional treatment
Presence of liver metastases on CT scan
Presence of at least one liver metastases of >20mm in diameter on the CT scan
Upper part of liver with left heart ventricle in field of view
Able to remain supine for 90 minutes in the PET-CT scanner
Ability to give study specific written informed consent

Exclusion criteria

Pregnant or lactating patients (positive pregnancy test)
Metal implants (eg pacemakers)
Body weight > 100 kg
Severe claustrophobia
Receiving chemotherapy less than 2 months prior to the first PET scan, except in the case of progression under chemotherapy than a 2 week interval is required.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	21-11-2014
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	23-05-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2015
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	NL48175.029.14