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2-[^{18}F]fluoro-2-deoxy-*D*-galactose PET/CT of hepatocellular carcinoma is not improved by co-administration of galactose

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ABSTRACT

Introduction: PET with [^{18}F]fluoro-2-deoxy-*D*-galactose (^{18}F-FDGal) is a promising imaging modality for detection of hepatocellular carcinoma (HCC). However, it can be difficult to distinguish small intrahepatic HCC lesions from surrounding liver tissue. Ut the competitive inhibition that galactose shows towards hepatic ^{18}F-FDGal metabolism, we tested the hypothesis that co-administration of galactose, at near-saturating doses, inhibits ^{18}F-FDGal metabolism to a greater extent in non-malignant hepatocytes than in HCC cells. This would increase the tumor to background ratio in the ^{18}F-FDGal PET scans with co-administration of galactose.
Methods: Three patients known to have HCC underwent two ^{18}F-FDGal PET/CT scans on consecutive days, one with and one without simultaneous constant intravenous infusion of galactose. On both days, ^{18}F-FDGal was injected in the beginning of a 45-min dynamic PET scan of the liver followed by a static PET scan from mid-thigh to the top of the skull starting 60–70 min after ^{18}F-FDGal administration. Parametric images of the hepatic metabolic function expressed in terms of hepatic systemic clearance of ^{18}F-FDGal were generated from the dynamic PET recordings.
Results: Co-administration of galactose did not give significantly better discrimination of the HCC lesions from background. Parametric images of the hepatic metabolic function did not add additional useful information to the detection of HCC lesions compared to the static images of radioactivity concentrations.
Conclusion: Co-administration of galactose did not improve the interpretation of the ^{18}F-FDGal PET/CT images and did not improve the detection of intrahepatic HCC lesions, either using static or parametric images.

1. Introduction

Transformation of normal cells to malignant cancer cells is often associated with increased metabolic requirements. For this reason, the radiolabelled glucose analogue [^{18}F]fluoro-2-deoxy-*D*-glucose (^{18}F-FDG) is widely used as a positron emission tomography (PET) tracer for diagnostic purposes in oncology. However, for the primary liver cancer hepatocellular carcinoma (HCC) ^{18}F-FDG PET has a limited sensitivity of around 60% [1–4].

Metabolism of the carbohydrate galactose and its radiolabelled analogue [^{18}F]fluoro-2-deoxy-*D*-galactose (^{18}F-FDGal) by the enzyme galactokinase [5] is almost exclusively confined to the liver. ^{18}F-FDGal has been validated as a PET tracer for non-invasive measurement of regional metabolic liver function [6–8]. Based on the hypothesis of increased activity of galactokinase in HCC, we showed that ^{18}F-FDGal PET/CT is a promising supplement to contrast-enhanced CT (ceCT) for the detection of HCC [9]. However, it can be difficult to distinguish small intrahepatic HCC lesions from surrounding liver tissue because the accumulation of ^{18}F-FDGal is high in normal as well as cirrhotic liver tissue [6–8].

We have previously shown that the hepatic metabolism of ^{18}F-FDGal in liver tissue was reduced significantly by co-administration of galactose due to competitive substrate inhibition of galactokinase [10]. We speculated that increased cell density in HCC lesions might lead to an overall elevated level of galactokinase that would be less inhibited by galactose than non-HCC tissue. We therefore tested the hypothesis that co-administration of galactose exerts a greater inhibition of ^{18}F-FDGal accumulation in non-malignant hepatocytes than in HCC cells and consequently increases the tumor to background ratio in ^{18}F-FDGal PET images. In addition, we combined static and dynamic PET imaging to examine if dynamic imaging of the metabolic capacity of ^{18}F-FDGal improves the diagnostic sensitivity compared to standard static PET imaging like it was shown for ^{18}F-FDG PET and small intrahepatic cholangiocarcinoma [11].

2. Materials and methods

2.1. Patients

Three male patients with HCC according to the EASL-EORTC guidelines [12,13] were enrolled in the study. Patient #1 was 72 years old and had cirrhosis on the basis of non-alcoholic steatohepatitis; patient #2 was 73 years old and had HCC of unknown etiology in a non-cirrhotic liver; patient #3 was 65 years old and had cirrhosis due to alcohol. In patients

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#1 and #2, HCC was confirmed by biopsies. Patients #2 and #3 had not received any treatment for HCC prior to participation. Patient #1 had received combined radiofrequency ablation and transarterial chemoembolization 19 months before the present study and stereotactic radiotherapy 7 months before. He had recurrence diagnosed by ceCT 2 weeks before the present study.

The study was approved by The Central Denmark Region Committees on Health Research Ethics and conducted in accordance with the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients. No complications to the procedures were observed.

2.2. Study design

On consecutive days, the patients underwent both a dynamic and a static ^{18}F-FDGal PET/CT scan each day - one day with and one day without simultaneous constant intravenous infusion of galactose. The patients fasted for at least 6 h before the studies but were allowed to drink water.

2.3. Galactose infusion

On the day with co-administration of galactose, a constant infusion of 2.3–2.6 mmol/min galactose was started one hour prior to ^{18}F-FDGal administration, initiated by a small priming bolus, and maintained until end of experiment. Blood concentrations of galactose deviated less than 5% from the mean values during each patient examination; mean values were 9.0 mmol/L blood, 7.3 mmol/L blood, and 7.1 mmol/L blood in patients #1, #2 and #3, respectively. This ensured near-saturation of galactokinase of approximately 90% as estimated from the Michaelis–Menten constant of 0.9 mmol/L blood in both healthy subjects [6] and patients with cirrhosis [8].

2.4. ^{18}F-FDGal PET/CT recording

The patient was placed in supine position in a 64-slice Siemens Biograph TruePoint PET/CT camera (Siemens AG, Erlangen, Germany). A topogram of the abdomen was performed for optimal positioning of the liver within the 21.6 cm transaxial field-of-view, and a low-dose CT scan (50 effective mAs with CAREDose4D, 120 kV, pitch 0.8, slice thickness 5 mm) was used for attenuation correction of PET emission data and anatomy. A bolus of 105–133 MBq ^{18}F-FDGal produced at the PET Centre [14] was administered intravenously at the start of a 45 min dynamic PET scan of the liver (list-mode acquisition). After voiding and starting 60–70 min after administration of ^{18}F-FDGal, the patient underwent a second low-dose CT from mid-thigh to top of the skull followed by static PET/CT recording of the same region with an acquisition time of 3 min/bed position (5–7 bed positions).

2.5. Reconstruction of PET data and image processing

PET data from the dynamic and static PET recordings, corrected for radioactive decay back to the start of the dynamic PET recording, were reconstructed using TrueX iterative algorithm with three iterations, 21 subsets and a Gaussian filter of 3.0 mm (static: matrix 168, $4 \times 4 \times 3$ mm^3 and dynamic: matrix 168, $4 \times 4 \times 2$ mm^3). Data from the

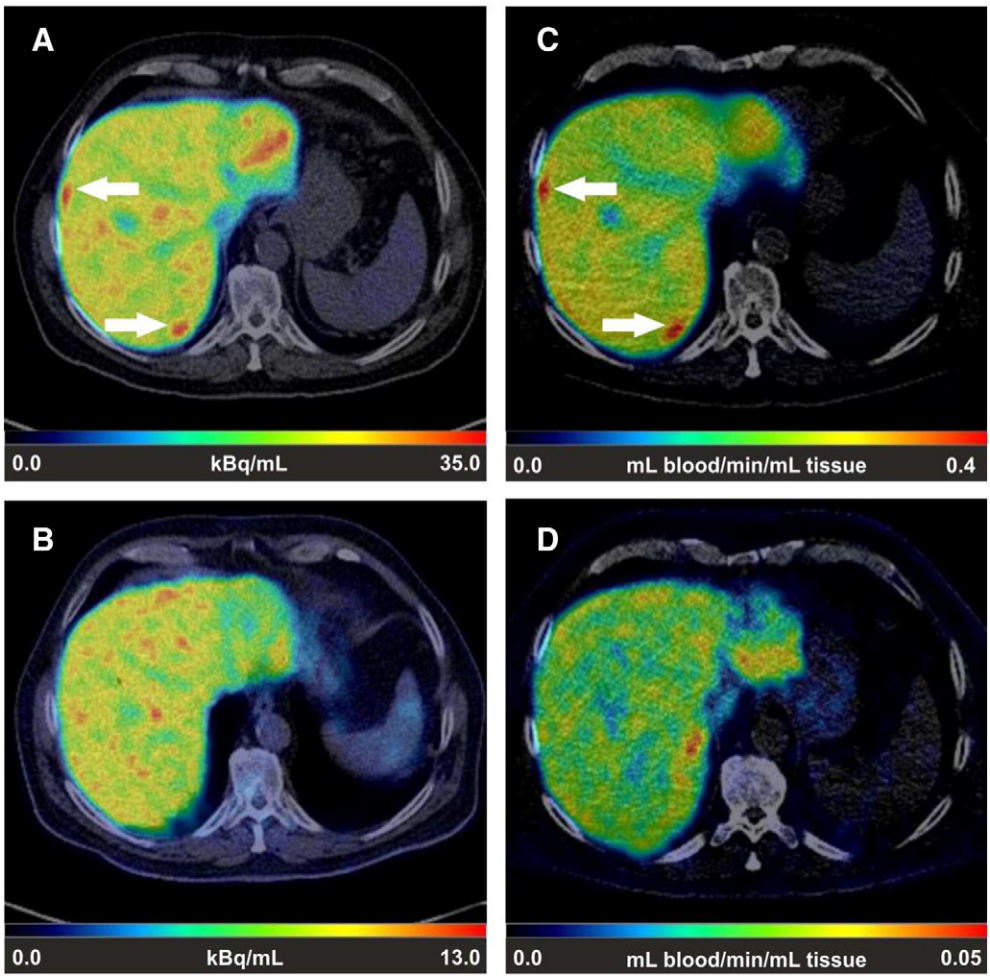

Fig. 1. Transaxial slices of ^{18}F-FDGal PET/CT images (patient #2), two HCC lesions are marked with arrows. Images of average radioactivity concentration, *C* (kBq/mL tissue) from static PET recordings without co-administration of galactose (**A**) and with co-administration of galactose (**B**). Parametric images of hepatic metabolic function expressed in terms of hepatic systemic clearance of ^{18}F-FDGal, *K* (mL blood/min/mL tissue) from dynamic PET recordings without co-administration of galactose (**C**) and with co-administration of galactose (**D**). Note the differences in the scale of the color bars for studies with and without galactose.