Monitoring response to transarterial chemoembolization in hepatocellular carcinoma using 18F-
Fluorothymidine Positron Emission Tomography

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Abstract

Accurate disease monitoring is essential following transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) due to potential for profound adverse event and large variation in survival outcome. Post-treatment changes on conventional imaging can confound determination of residual/recurrent disease, magnifying the clinical challenge. Based on increased expression of thymidylate synthase (TYMS), thymidine kinase-1 (TK-1) and SLC29A1 (Equilibrative nucleoside transporter 1, ENT1) in HCC compared with liver tissue, we conducted a proof of concept study evaluating the efficacy of 18F-fluorothymidine (18F-FLT)-PET to assess response to TACE. As previous PET studies in HCC have been hampered by high background liver signal, we investigated if a temporal-intensity voxel-clustering (“Kinetic Spatial Filtering”) (KSF) improved lesion detection.

Methods A tissue microarray (TMA) was built from 36 HCC samples and matched surrounding cirrhotic tissue and was stained for thymidine kinase-1 (TK-1). A prospective study was conducted; eighteen patients with a diagnosis of HCC by American Association for the Study of Liver Diseases criteria (AALSD) who were eligible to treatment with TACE were enrolled. Patients underwent baseline conventional imaging and dynamic 18F-FLT-PET/KSF followed by TACE. Repeat imaging was performed 6-8 weeks post TACE. PET parameters were compared with modified-Response Evaluation in Solid Tumours (mRECIST) enhancement-based criteria.

Results Cancer Genome Atlas analysis revealed increased RNA expression of TYMS, TK-1 and SLC29A1 in HCC. TK-1 protein expression was significantly higher in HCC (p<0.05). The sensitivity of 18F-FLT-PET for baseline HCC detection was 73% (SUVmax of 9.7 ± 3.0; tumour to liver ratio of 1.2 ± 0.3). Application of KSF did not improve lesion detection. Lesion response following TACE by mRECIST criteria was 58% (14 patients with 24 lesions). A 30% reduction in mean 18F-FLT-PET uptake was observed following TACE correlating to an observed PET response of 60% (n=15/25). A significant and profound reduction in radiotracer delivery parameter, K1, following TACE was observed.

Conclusion 18F-FLT-PET can differentiate HCC from surrounding cirrhotic tissue, with PET parameters correlating with TACE response. KSF did not improve visualization of tumour lesions. These findings warrant further investigation.
INTRODUCTION

The recommended treatment option for intermediate stage hepatocellular cancer (HCC) is transarterial chemoembolisation (TACE), which involves the delivery of a cytotoxic agent commonly mixed with lipiodol followed by selective embolization of the tumoural arterial supply(1). The typical vascular pattern of HCC on contrast enhanced-CT or MRI is early arterial enhancement followed by “washout”. Whilst both contrast-enhanced CT and MRI are widely used to assess response post TACE, there is uncertainty in their ability to detect viable disease post TACE(2). Modified RECIST criteria, which measure changes in arterial enhancement as a marker of residual viable tumour, is a more accurate measure of tumour response to treatment than standard RECIST and is routinely used in the assessment of HCC(3). However, lipiodol deposition can induce beam-hardening artefact and obscure enhancement on arterial phase, reducing the sensitivity of CT post TACE. With MRI, coagulative haemorrhagic necrosis may lead to high T1 signal making enhancement assessment difficult(4).

PET imaging has been evaluated in HCC for staging and response assessment(5). Studies investigating 18F-fluorodeoxyglucose (18F-FDG) in HCC show limited sensitivity (50 –70%) due to similar activities of glycolytic enzymes and glucose 6-phosphatase in liver and well-differentiated HCC resulting in near equivalent uptake of 18F-FDG(6). Imaging with single agent 11C-acetate and 11C-, 18F-choline are similarly limited, culminating in the exploitation of dual-tracer techniques to improve sensitivity and specificity(7).

3′-Deoxy-3′-18F-fluorothymidine (18F-FLT) is a surrogate marker of proliferation, with uptake reflecting the activity of thymidine kinase (TK-1) whose expression correlates with ex vivo proliferation biomarkers(8). Unlike 18F-FDG, the uptake of 18F-FLT is more specific for proliferation and is unaffected by inflammation, a particular concern as HCC tumours develop within a pro-inflammatory milieu(9). To date a single study of 18F-FLT-PET in HCC indicated that 69% of patients had uptake higher than background liver, whilst the remaining lesions were either photopaenic or of mixed uptake(10). However, the patient group was heterogeneous including cholangiocarcinoma, and no information was given regarding therapy response. To improve lesion detection, we have previously applied a temporal voxel-clustering approach—Kinetic Spatial Filter (KSF)—for removing normal, physiological hepatic 18F-FLT uptake and to visualise specific uptake (i.e. uptake due to phosphorylation) in liver metastases(11). Briefly, the KSF compares the time-activity curves
(TACs) of each voxel with the TAC of predefined tissue classes such as liver and tumour. Voxels classed as “liver-like” are excluded, thereby removing areas of physiological uptake unrelated to 18F-FLT retention.

This study evaluates the clinical utility of 18F-FLT-PET in assessing TACE response in HCC. We first reviewed RNA expression of key targets in the metabolism of FLT using large published datasets of HCC. We then investigated the tissue expression of TK-1 in HCC and surrounding cirrhosis, an important consideration in developing a tracer paradigm that will effectively differentiate cirrhotic tissue and HCC. Finally we undertook a prospective study using dynamic 18F-FLT-PET to both visualise the tumours and use as a response biomarker, incorporating application of the KSF and kinetic modelling.
MATERIALS AND METHODS

Bioinformatics Analysis

RNA-sequencing dataset containing 371 HCC and 50 non-malignant tissue from The Cancer Genome Atlas (TCGA) project was measured from Illumina HiSeq 2000 RNA Sequencing platform. The RSEM normalized data was downloaded from UCSC Xena (http://xena.ucsc.edu/). Differential gene expression of TK1, TYMS and SLC29A1 comparing tumour and non-malignant tissue were performed using ‘ggplot2’ package and ‘t.test’ function in R 3.5.2.

Tissue Microarray

Immunohistochemistry for TK-1 (1:100, AbCam, Cambridge) was performed on a tissue microarray (TMA) from patients with a histological diagnosis of HCC (n=36)(Supplemental Methods and Materials). A trained histopathologist (FM) blinded to the clinical data scored all cases manually using the immunohistochemical score(12).

Prospective Study Design

Eighteen patients with HCC were prospectively enrolled. Patients received standard TACE with liposomal doxorubicin emulsified in lipiodol followed by embolisation with gelatin sponge particles. Baseline staging included contrast CT and/or MRI liver conducted 28 days prior to TACE and the same imaging modality repeated 6-8 weeks following TACE for treatment response, and then 3-monthly until disease progression. Modified RECIST (mRECIST) for HCC(13) was documented by a single experienced hepatobiliary radiologist (PT) (Supplemental Methods and Materials). .

Image Analysis

Lesions on 18F-FLT-PET corresponding to those on the CT or MRI greater than 10mm, and showing an increased uptake were considered as target lesions and used for analyses on both the PET/CT and CT or MRI, before and after treatment.
Consecutive regions of interest (ROI) were manually defined on the summed images and encompassed the whole tumour for SUV analysis. 18F-FLT radioactivity concentration within the ROIs was normalised for injected radioactivity and body weight (grams) to obtain mean and maximum SUV at 60 minutes (SUV$_{60\text{mean}}$, and SUV$_{60\text{max}}$) on baseline and post-treatment 18F-FLT PET/CT studies. The percentage change in SUV in both SUV$_{\text{mean}}$ and SUV$_{\text{max}}$ was calculated for each target lesion visible on baseline imaging as; (SUV$_{\text{post}}$ – SUV$_{\text{pre}}$)/SUV$_{\text{pre}}$. In each case, a 3cm ROI was placed in the liver in a tumour-free area to measure background liver SUV$_{\text{mean}}$, and the tumour/liver (T/L) ratio (Tumour SUV$_{\text{max}}$/Liver SUV$_{\text{mean}}$) determined.

**Quantitative Analysis**

A metabolite-corrected image-derived arterial input function was implemented during kinetic modelling of data with a two-tissue compartmental model (Supplemental Material and Methods – Quantitative Analysis).

**Statistical Analysis**

As this was a pilot study, no formal power calculation was undertaken. Summary statistics of the associations between PET parameters and clinical outcome were determined. Due to the small sample size, patients were grouped as responders (complete and partial response, CR and PR) or non-responders (stable disease or progressive disease, SD and PD). The relationship between kinetic parameters and response was evaluated using Wilcoxon rank tests. Chi-squared test was used to evaluate utility of the tracer pre- and post-TACE therapy. Concordance was determined using Cohen's kappa analysis. $P \leq 0.05$ was considered significant. All statistical analyses were conducted using SPSS statistical package version 22 (SPSS Inc., Chicago, IL, USA).
RESULTS

Expression of Enzymes Involved in Thymidine Metabolism increased in HCC Compared with Cirrhotic tissue

Using RNA-sequencing data from The Cancer Genome Atlas we observed a significantly higher expression of *TYMS*, *TK-1* and *SLC29A1* in tumour tissue (n=371) compared to adjacent non-malignant tissue (n=50; p<0.05) (Supplemental Figs. 1A, B and C). Using a TMA we observed a significantly higher TK-1 expression in HCC (median immunohistochemical score 33, range 0 - 300) compared to the surrounding parenchyma (score 0, range 0 – 50), suggesting that 18F-FLT has the potential to differentiate HCC from surrounding cirrhotic liver (p=0.004) (Supplemental Figs. 2 A, B and C).

Patient Characteristics

Eighteen patients were enrolled (16 men and 2 women) with 16 patients completing the study. (Table 1). Median age was 68 years (range 42–79years). All patients received TACE for intermediate stage disease. Three patients had had previous TACE and were undergoing retreatment for residual active disease; the remaining patients were treatment naïve.

HCC is Visible Above Background Liver Using 18F-FLT-PET Imaging

Twenty-six liver lesions, median 29.5mm (range 10-117mm) were identified on conventional imaging; five had baseline MRI and the remainder CT. On PET visual analysis, 19 lesions were visible above background liver (73% sensitivity)(Figs. 1A-F).

All lesions were included in analysis. The mean SUV$_{60,\text{mean}}$ (±SD) and SUV$_{60,\text{max}}$ on baseline imaging were 6.5 (±1.9) and 9.7 (±3.0), respectively. The mean SUV$_{60,\text{mean}}$ of the background liver was 6.1 (±0.9). A significant difference was observed between SUV$_{60,\text{max}}$ of the cancer compared to surrounding, non-cancerous liver tissue (p=0.02), with the mean tumour to liver (T/L) ratio being 1.2 (±0.3), confirming that uptake in HCC was above cirrhotic background activity, enabling visualization on 18F-FLT-PET scans in most cases.

Application of Kinetic Filter Does Not Improve Visualization of HCC on Cirrhotic Liver Background

Background liver activity was completely filtered out in 12/16 patients; 4/16 patients retained partial background liver activity. KSF did not improve image visualisation above that of PET/CT imaging; 11 of the 26
lesions (42%) were visible following application of KSF compared with 19 lesions without KSF (Figs. 2A-F). Small lesions typically had a homogeneous appearance, whereas larger lesions were characterised by perilesional tracer uptake with no measurable FLT trapping in the necrotic centre of tumour. Of the 15 lesions not visualised by the KSF, 9 (60%) were <30 mm; 3 lesions had higher tissue activity than the average for HCC predetermined by the KSF and the remaining lesions did not retain radiotracer following application of the filter. As KSF is associated with removal of delivery components within the data, there was a mean (range) signal reduction in the tumours at baseline of 81% (18–100%) relative to the unfiltered images. The mean reduction in background activity in the liver was 98% (83–100%), resulting in an improved T/L ratio of 11.1 ± 17.7.

**18F-FLT Uptake Parameters and Clinical Outcome**

In terms of response to TACE according to mRECIST criteria, 24 lesions were assessable; two lesions were not assessable (one patient withdrew consent following baseline PET). Response was observed in 14/24 (58%) and non-response in 10/24 (42%) lesions. There was a median overall reduction in 18F-FLT-PET/CT SUV$_{60}$, mean (−29.5% ± 31.4%) and SUV$_{60, max}$ (−18.5% ± 27.5%) following TACE. Previous test–retest reproducibility studies in breast cancer considered changes in 18F-FLT SUV of more than 20% as significant (SD: 10%–15%)(14). Using a 20% reduction in SUV$_{60, mean}$ to define PET response led to categorization of lesional response in 60% (N=15/25) and non-response in 40% (n=10/25). Using Cohen’s kappa measures, there was good concordance between lesional PET response and lesional mRECIST (κ 0.66, p<0.001, 95% CI 0.35 – 0.97).

**Kinetic Modelling Illustrates Significant Reduction in 18F-FLT Uptake and Retention Following TACE**

The analysis of 18F-FLT dynamic data with a two tissue compartmental model resulted in physiologically relevant kinetic parameters (N=14) (Table 2)(15). There was a significant reduction in mean $K_1$ values from baseline, $0.3±0.1$ (mL/min/g), compared to post-treatment, $0.13 ± 0.05$ (p<0.001). This is consistent with the abrupt cessation of blood flow to the tumour following embolization resulting in reduced transport of 18F-FLT to the tumour. While all tumours showed some degree of reduction in $K_1$, the change was greater in responders (66% reduction) versus non-responders (50%), p=0.03 (Supplemental Fig. 3A). Baseline SUV$_{60, mean}$ and baseline $K_1$ were significantly correlated (Pearson’s correlation coefficient 0.5, p=0.04) and a significant difference was observed in $K_1$ at baseline $0.09 ± 0.03$ (mL/min/g) compared to post-TACE imaging,
0.04 ± 0.02 (p<0.001). In responders, baseline $K_i$ and $v_B$ were greater compared to non-responders (Supplemental Figs. 3B and C)(p<0.05).
DISCUSSION

There is still no single tracer recommended by international guidelines for either diagnosis or response assessment in HCC(1). The main limitation of the studied tracers has been poor tumour-to-background liver ratio resulting in a dual tracer approach for visualizing HCC, which is time-consuming and exposes patients to significant radiation(5). We hypothesized, that as 18F-FLT uptake is specific for tumour proliferation, tracer uptake will not be affected by the presence of inflammation(16). Moreover, we investigated the utility of KSF to improve visualization of HCC by removing background liver activity.

In order to address the hypothesis that tumour 18F-FLT uptake will change predictably with effective treatment, we first assessed the mRNA expression of factors responsible for handling 18F-FLT. TYMS catalyses the last step in the de novo synthesis of thymidine monophosphate (TMP) whilst TK-1 catalyses synthesis of TMP via the salvage pathway. TK-1 impacts on 18F-FLT cellular trapping and is a surrogate marker of proliferation(17). Moreover, we have shown that with TYMS inhibition, 18F-FLT uptake increases due to redistribution of the membrane transporter SLC29A1 to the plasma membrane(18). Expression levels of TYMS, TK-1 and SLC29A1 were all markedly upregulated in HCC compared to normal liver; we confirmed marked upregulation in protein expression of TK-1 in HCC compared to surrounding matched cirrhotic tissue consisting of both regenerative and dysplastic nodules suggesting that 18F-FLT could be useful in differentiating HCC from surrounding cirrhotic tissue.

Our prospective 18F-FLT-PET study illustrated that the majority of intrahepatic lesions, had increased tracer uptake above background liver consistent with the TMA findings. To improve HCC visualization, we applied the previously validated KSF(19,20). However, fewer lesions were detected with the filter than with standard PET/CT imaging; the majority of small lesions, <3cm, were filtered out. Possible explanations are: (i) the KSF compares voxel temporal profiles with standard tissue profiles and both liver and lesion voxel profiles were highly variable in our group; (ii) the cirrhotic background has a high relative uptake which, in combination with (i), reduces the ability of the KSF to effectively discriminate HCC from the proliferating, background liver, (iii) partial volume effects may contribute to filtering out of small lesions.
When considering 18F-FLT-PET imaging for lesion detection, our findings are in keeping with Eckels and colleagues who reported a 72% sensitivity of 18F-FLT in visualizing HCC with similar median SUV and T/L ratios(10). Similar sensitivities have been reported with 11C-acetate-PET and with a dual tracer approach with 18F-FDG and 11C-acetate, 75% and 73%, respectively(21,22). However, Ho and colleagues report single tracer sensitivity of 87% with 11C-acetate, increasing to 100% sensitivity using two tracers(23). These differences in diagnostic sensitivity may be a reflection of the subgroup analysis undertaken in the Ho paper. Overall, the literature does suggest improved diagnostic sensitivity using a dual tracer approach, which motivates the development of alternate tracers for the detection of HCC.

We investigated the role of dynamic 18F-FLT-PET as a predictor of TACE response. The radiologic response to TACE by mRECIST was 54%, and by PET was 60%, with good concordance between imaging modalities observed. Cascales-Campos and colleagues considered using 18F-FDG-PET to assess response to TACE prior to liver transplantation(24). The authors describe a reduction in 18F-FDG uptake correlating with degree of necrosis on pathologic examination of the explanted liver, and other investigators have considered minimum SUV cut-off values for defining response to therapy(25). In a retrospective study, Park and colleagues investigated the utility of a dual tracer approach with 18F-FDG and 11C-acetate in predicting response to TACE. They did not investigate concordance between the imaging modalities but observed that the ratio of 18F-FDG to 11C-acetate predicted response to TACE determining a cut off from ROC analysis(7). We selected a 20% reduction in SUV_{60,max} to indicate response, a cut-off extrapolated from breast cancer studies(26). Larger studies are needed to define a more accurate cut-off for HCC than was possible to derive from our small data-set.

A key strength of this study is that dynamic PET imaging allows us to establish the basis of the PET signal change in HCC, considering that TACE acutely impacts on blood flow. In line with our hypothesis, we report a significant reduction in K_1 following TACE, illustrating abrupt reduction in tissue perfusion. This is in sharp contrast with anti-angiogenic chemotherapy where an increase in the K_1 due to vessel normalization and reduced interstitial pressure can accompany response(27). Dynamic studies using 11C-acetate report a reduced K_1 in HCC lesions supplied by the hepatic artery compared with benign lesions supplied by the portal vein as the radiotracer concentration time-course is initially delayed in the portal vein as passes through the splanchnic circulation(28). Huo and colleagues reported that because of the differential time-course of
radiotracers circulating through the hepatic artery or portal vein, lesions supplied by the hepatic artery will reach “stable concentration” of radiotracer earlier and at a higher peak following injection; hence arterialized lesions will have a lower $K_i$ compared to benign lesions that are supplied predominantly by the portal vein (29). $K_i$ is the metabolic flux constant and it is related to the phosphorylation of the thymidine in the tissue (30). It has previously found to be correlated to 18F-FLT SUV (31); and our results illustrate similar correlation.

Moreover, we report baseline $K_i$ and $v_B$ to be predictive of TACE response to treatment suggesting that responding tumours are more actively proliferating and have higher perfusion suggestive of higher vascularity.

Study limitations include small sample size and lack of correlation of PET uptake parameters with histology. If subjects had whole body imaging full assessment of extra-hepatic disease could be performed; correlation of PET kinetic parameters with SUV means that future whole body static imaging would be supported. In addition manual VOIs could not be used to determine thresholds as components of the tumour were close to background liver activity. In addition, some lesions became isointense/photopenic relative to background on follow-up PET imaging.

In summary, we have shown that TK-1 expression is significantly higher in HCC compared to surrounding cirrhotic tissue supporting the use of 18F-FLT-PET. High 18F-FLT-PET uptake is seen in the majority of HCC, however application of KSF did not improve visualization due to high and variable SUV both in tumour and background cirrhotic liver. Imaging proliferation with 18F-FLT-PET may be used to predict response to TACE in this small case series. Whilst this study is a pilot study, the results generated are provocative and should be taken forward to larger prospective trials correlating with outcome.

FIGURE LEGENDS

FIGURE 1. Axial CT, Fused and FLT PET images pre-(A, B, C) and post-(D, E, F) TACE show focal HCC lesion (red outline) with increased FLT uptake at baseline and reduction post TACE.

FIGURE 2. Axial CT, unfiltered PET and filtered PET images pre-(A, B, C) and post-(D, E, F) TACE show focal HCC lesion (red outline) with increased FLT uptake at baseline and reduction post TACE. Images B and E indicate PET images prior to application of KSF where at baseline (B) HCC is visible above background. Following application of the filter, the tumour is mostly filtered out (C). In the post TACE images, the HCC is photopaenic compared to surrounding liver prior to application of the filter (E). Following application, the background liver activity is removed and the HCC remains visible (F)

DISCLOSURES
No authors have any conflicts of interest to declare.

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KEY POINT QUESTION

Does dynamic 18F-FLT-PET allow accurate visualisation of HCC?

PERTINENT FINDINGS

18F-FLT-PET can differentiate HCC from surrounding cirrhotic tissue, with PET parameters correlating with TACE response.

IMPLICATIONS FOR PATIENT CARE

18F-FLT-PET can accurately detect HCC and should be further investigated, particularly for assessment of response.

REFERENCES


Scarpelli M, Simoncic U, Perlman S, Liu G, Jeraj R. Dynamic (18)F-FLT PET imaging of spatiotemporal changes in tumor cell proliferation and vasculature reveals the


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Table 1. Imaging features of HCC
lesions

Lesion untreated
Photopenic lesion
Patient died of unrelated illness
Patient underwent liver transplant

SUV – standard uptake value
preRx – pretreatment
Table 2. Baseline Dynamic PET parameters (N=14)

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