A Proof-of-Principle Multiparametric in vivo Study of Tumor Microenvironment using a MRI Compatible PET Insert.

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OBJECTIVE To demonstrate the possibility of using simultaneous non invasive PET and MRI to investigate microscopic, functional changes in tumor microenvironment.

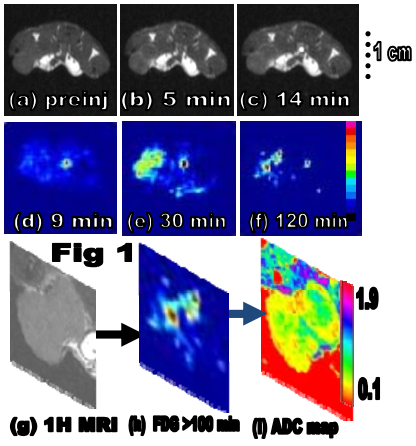
INTRODUCTION The ability to assess therapeutic response to cancer treatment is an essential requirement for the development of new types of therapeutic agents. In this perspective both PET and MRI provide unique windows into tumor microenvironment and can potentially probe therapy induced local functional and anatomical changes. The availability of MR compatible PET inserts [1] has provided the ability to image tumors in both modalities simultaneously without the need to perform complex and time consuming image post processing. Here we show that it is possible to design and implement an in vivo imaging protocol that allows (a) simultaneous acquisition of dynamic contrast enhanced (DCE) images and dynamic ^{18}F-FDG PET images; (b) diffusion weighted imaging (DWI); (c) basic anatomical imaging. Integrating the parts of this multiparametric data provides a quantitative assay that correlates FDG uptake, tumor hypoxia, cell proliferation and blood perfusion [2] as well as providing a fundamental template for similar clinical studies.

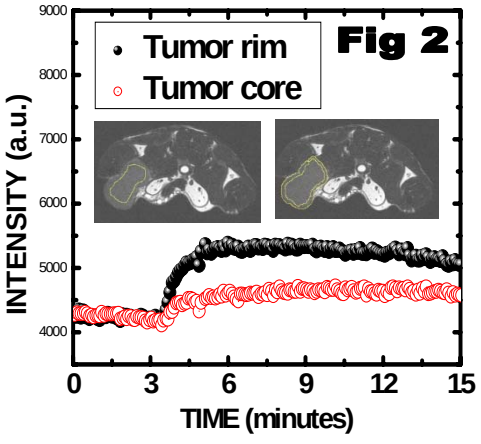
METHODS CEA tumor cells were implanted in the left groin of C57 mice two weeks prior to imaging. Imaging sessions begin with the insertion of a 26G tail vein catheter loaded with a mixture of PROHANCE (0.1mmoles/kg) and ^{18}F-FDG (200μCi). The anesthetized mice (isofluorane/O_2) mice are placed in an animal holder and using a computer controlled positioning device (Aereotech) are placed at the center of the magnet and the PET detector (as described in [1]). Normal body temperature (37°C) is maintained with an air heating system; respiration is monitored using a transducer coupled to a respiration pillow (BIOPAC). MRI data is collected on a 7T Bruker Biospec scanner using the following pulse sequences: (A) DWI: Spin Echo sequence with diffusion weighted module using and 5 b-values (0-1000 mm/sec^2) with δ=3 msec, Δ=30 msec; three axial slices of 0.75 mm thickness and in-plane resolution of 250μm^2; (B) DCE: T_1 weighted multi spin echo sequence; two slice packages (3 axial slices covering the iliac artery bifurcation and 5 slices covering the tumor region); 0.75 mm thickness and 250μm^2 in plane resolution. A temporal resolution of 4.8 sec/image with a total number of 300 repetitions was employed in order to collect a complete time series with sufficient sampling of the arterial input function (AIF); (D) anatomical high resolution axial multi slices were obtained using a multi spin echo T_2 weighted imaging sequence; 17 axial slices with thickness 0.75 mm and 100μm^2 in-plane resolution. In all cases (except DCE) respiration triggering was employed to reduce motion artifacts. PET images were acquired after injection of radiolabeled FDG for a total time of 140 minutes (3-5 minute scans). The dynamic acquisition of ^{18}FDG images was simultaneous with the MR DCE. Except for basic normalization of detector efficiencies using a uniform cylindrical phantom, no other corrections were applied to the PET data. The images were reconstructed using a fully 3D ML-EM algorithm.

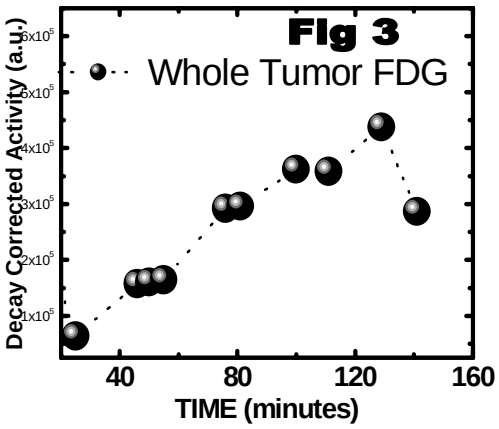
RESULTS Fig 1 shows three DCE images (a) pre injection (b) 5 minutes and (c) 14 minutes post injection; the corresponding geometrical PET slices at (d) 9 min (e) 30 min post injection and (f) 120 min post injection; and a stack of images representing blow ups of the tumor region (g) anatomical; (h) late time ^{18}FDG and (i) apparent diffusion coefficient (ADC) as obtained from the DWI data (values are expressed in 10^{-4} mm/sec^2). Plotted in Fig 2 are the image intensities of two different regions of interest (tumor rim and tumor core) as a function of time after injection. The anatomical reference images with corresponding ROIs are shown in the inset. Finally, in Fig 3 the decay corrected ^{18}F activity of the whole tumor is plotted as a function of time after injection of the prohance/FDG mix.

DISCUSSION Dynamic data was acquired simultaneously using both MRI and PET after injection of a mixture of prohance and ^{18}FDG. Although the pharmacokinetics of the two compounds is obviously different due to the different physiochemical properties (prohance is biologically inert while FDG is strongly affected by local metabolism), it can provide relevant functional information. The anatomical reference image was used to identify relevant tissue structures and to graphically select the regions of interest (for both MRI and PET). The DCE data was collected in order to obtain time series of quantitative data which was fitted using a standard two compartment model (Tofts) providing parametric maps (not shown here) directly associated with local vasculature. The data as plotted in Fig 2 demonstrates the difference between different regions in the tumor. The voxel by voxel apparent diffusion coefficient was obtained by fitting the DWI data using a standard exponential behavior. The corresponding parametric tumor image depicting the different ADC values shows local changes that indicate differences in cellular structure and integrity. ^{18}FDG images were acquired throughout the experiment and the data was compared to MR functional data (tumor ADC map and DCE time series) to investigate correlations that might provide insight into tumor microenvironment. The image stacks shown indicate a degree of correspondence between higher ADC tumor values and longer time retention of ^{18}FDG.

CONCLUSION The ability to discriminate anatomical features in vivo and assess functional activity using different techniques in the same imaging session was established to be feasible. The imaging protocol was designed in order to provide (1) quantitative DCE data that can be used to obtain quantitative angiogenic data on a case to case basis (by obtaining the contrast agent AIF for each and every subject) (2) quantitative ADC maps that enables the characterization of cellular integrity and function; and finally (3) dynamic ^{18}FDG maps that can be correlated with other MR parametric information. Taken together this information provides an excellent quantitative characterization of the tumor microenvironment. In addition by demonstrating that DCE data can be acquired simultaneously with ^{18}FDG data we are establishing the possibility of performing cross modality studies such as: (a) ^{19}F MRS-^{18}F PET hypoxia investigations using labeled nitroimidazoles [3]; (b) obtaining quantitative PET assays by using the high temporal resolution of MRI pharmacokinetics to assess the AIF of different tissues under investigation.







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