No. 49

IMAGING ANGIOGENESIS: CORRELATION OF UPTAKE OF A NOVEL TRACER TO MICROVESSEL DENSITY IN XENOGRAFT MODELS

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The role of angiogenesis in cancer is well understood and it is documented that growth beyond 1-2mm^3 of a solid tumour and their metastases requires persistent new vessel growth. As such, angiogenesis is used as a marker for tumour growth and progression. At present, the gold standard method of investigating angiogenesis in tumour tissue is by the histological technique of microvessel density (MVD) counting of tissue samples, but this technique has well known weaknesses. The targeting of receptors expressed selectively on endothelial cells in areas undergoing neo-vascularisation is an approach to the diagnosis of cancer. The receptor studied in this work has limited tissue distribution, with highest levels of expression achieved in growth factor activated endothelium during angiogenesis. Substrates for this receptor are well known, and the chosen vectors are small peptides containing an RGD (Arg-Gly-Asp) motif in a configuration that allows high affinity (nM range) and specific binding to the receptor. Based on these peptides several chelate-peptide conjugates have been synthesised and screened, with 99mTc-NC100682 demonstrating good synthesis, acceptable radiolabelling, pharmacokinetics and *in vivo* efficacy.
The objective of this work was to determine how the level of angiogenesis related to the gamma camera images obtained using 99mTc-NC100682. Therefore, it was necessary to determine the amount of angiogenesis in experimental tumours (MVD/mm2) and correlate this to biodistribution data (%ID and % retained).
Experimental xenograft models bearing H69, PC3, MDA-MB-231, T84, LLC or VX2 tumours were injected with 100MBq of 99mTc-NC100682 and euthanised and dissected 120 minutes post injection. Tumours were counted for radioactivity to determine %ID and then processed according to standard histological procedures. Slices from each tumour type were analysed for MVD to quantify the amount of angiogenesis. Each of the experimental tumours investigated had different levels of angiogenesis, with highest-MVD seen in T84>LLC>MDA-MB-231>W256>PC3>H69>VX2. A correlation was seen between MVD/mm2 and %ID and also % retained, with increased uptake and retention seen with increasing MVD.
In conclusion, the results demonstrate that there is a direct relationship between %ID and MVD. The data also supports the specificity of 99mTc-NC100682 for targeting a receptor known to be up regulated during angiogenesis.

No. 50

18F-FIAU IMAGING IN DOGS WITH POSITRON EMISSION TOMOGRAPHY

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Objective: FIAU is of interest as a potential tracer to monitor HSV-tk gene expression. This study was performed to investigate the biodistribution and DNA uptake of 18F-FIAU, (1-(2'-deoxy-2'-fluoro-1-β-D-arabinofuranosyl)-5-iodouracil) in normal dogs. For labeling of FIAU, 18F is a more desirable isotope than 124I because it is more widely available, has a more favorable energy profile, and superior dosimetry.
Methods: 18F-FIAU was synthesized as previously reported and four normal dogs were injected with an average activity of 303 MBq. Three dogs underwent dynamic imaging for 60 minutes over the upper abdomen followed by whole body imaging until about 2.5 hours. The fourth dog was not scanned and was euthanised at 60 minutes post injection. Blood and urine samples obtained at different intervals were analyzed for clearance and metabolism using HPLC. Tissue samples were collected at the end of the experiment and acid extractions were performed to study incorporation into DNA.
Results and Discussion: HPLC analysis of blood and urine samples taken at 60 minutes showed that more than 78% and 63% of the radioactivity was unmetabolized FIAU, respectively, demonstrating resistance to metabolism. Tissue to muscle ratio from tissue and image analysis showed slightly higher uptake in organs with high proliferation rate such as small intestine (tissue to muscle ratio, mean: 1.87) and marrow (mean: 1.60) compared to nonproliferative organs such as heart (mean: 1.12), and lung (mean: 1.10). High uptake was seen in the bile (mean: 18.37) demonstrating hepato-biliary excretion of the tracer. Extraction analysis of tissue samples showed that 50% of the activity in small intestine, 70% in marrow and less than 18% in heart, liver and muscle was incorporated into DNA.

Conclusion: Our results demonstrated that FIAU is resistant to metabolism and moderately incorporates into DNA in proliferating tissues. These results support the use of FIAU to image the distribution of HSV-tk reporter gene in studies of gene therapy. However, incorporation into DNA of normal tissues may need to be taken into account when FIAU is used to track reporter gene activity. Studies in humans are needed to determine if differences in metabolism may lead to alter imaging properties for therapeutic studies.

No. 51

DESIGN OF A HIGH RESOLUTION SMALL ANIMAL OCTAGONAL PET SCANNER: PRELIMINARY STUDIES

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Introduction: We present a preliminary study on the design of a high resolution small animal octagonal positron emission tomography (PET) scanner, based on Monte Carlo simulations. The purpose of this study is to evaluate the impact of several critical design parameters on the reconstructed image quality, as well as the calculation of the system matrix for iterative image reconstruction based on statistical models.
Materials and Methods: The basic tomograph design consists on eight planar detector blocks in octagonal configuration. The number and size of the individual crystals, as well as the exact position of each block and the size of the angular gaps between them are some of the variables of the design optimization procedure. For the depth of interaction effect simulation LSO scintillator characteristics have been used, but inter crystal gamma or light scatter is not enabled. Activity distributions are generated based on several classes of parametric volumes placed in the field of view (FOV). Coincidence data are stored in histogram mode without rebinning, and coincidences are allowed among one detector and the three or five opposites, resulting in a total of 12 or 20, respectively, possible detector block pairs.
When sinogram-based reconstruction methods are used, coincidence

data can be stored in sinograms similar to the ones proposed by Defrise, et al. In octagonal configurations without rotation, each sinogram is composed of characteristic diamond-shaped sections, corresponding to each detector block pair and separated by strips whose width size is related to the angular gap between detector blocks. Non-uniformity artifacts due to sinogram discretization is corrected by normalization. FBP and iterative image reconstruction algorithms based on the maximum-likelihood expectation-maximization (MLEM) and Bayesian approaches are employed, and the system matrix is calculated using the same Monte Carlo approach. Sparse matrix techniques are implemented in order to efficiently represent this matrix structure and achieve fast image reconstruction.

Results and Discussion: The figure shows the results obtained with a simulated phantom. In the direct sinogram, the stripes produced by the angular gaps in the detector geometry are evident. If these gaps are not corrected, they produce large artifacts in the filtered back projection reconstructed image. Iterative reconstructions with the appropriate system matrix however can deal with the lack of information in these regions, producing correctly reconstructed images.

Conclusions: An octagonal tomograph configuration represents a good compromise between design simplicity, low cost and good sensitivity in comparison to small animal PET scanners employing two rotating detector blocks. The FOV diameter can be increased by separating the detector blocks. In this case, iterative image reconstruction algorithms can produce images which are not affected by the presence of gaps, in contrast to the FBP-based reconstruction methods.

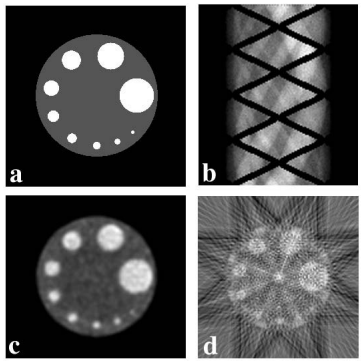

Figure 1. *(a) Simulated phantom, Axial view. (b) Direct sinogram from the Defrise set. Note the characteristic stripes generated by the angular gap in between detector blocks. (c) MLEM reconstruction using the system calculated from the simulations. (d) FBP reconstruction from rebinned sinogram without any gap removal technique; window level has been stressed in order to enhance the artifacts due to the sinogram strips.*

No. 52

HIGH TEMPORAL RESOLUTION BLOOD INPUT FUNCTION MEASUREMENT WITHOUT BLOOD SAMPLING USING THE BETA MICROPROBE IN THE ANAESTHETIZED RAT

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Introduction: Radiotracer studies in living animals require the venous injection of a radioactive tracer. To extract relevant biochemical information, time activity curves in the regions of interest are mathematically modeled on the basis of compartmental models which describe the biochemical pathways of the tracer from blood to biological target. For instance, local metabolic rate of glucose can be quantitatively determined after injection of 2-deoxy-2-[18F]fluoro-D-glucose (FDG) (a radiolabeled analogous of glucose) by modeling the kinetics rate constant that define the passage of the tracer from one compartment to another. This model involves the knowledge of the time activity curve in plasma- also called "input function"- that determines the availability of the tracer to the regions of interest. Usually the input function is measured by repeated blood sampling. In small animals, this involves labor-intensive manual withdrawals which present several drawbacks: a temporal resolution limited to five to ten seconds between each sample which affects the accuracy of the input function, the need to collect relatively large amount of blood, and the repeated radioactive exposure of the persons in charge of blood sampling. In this study we evaluated the measure of on-line input function with a radiosensitive Beta Microprobe inserted in the femoral artery of a rat associated or combined to an additional probe to quantify the background activity.

Methods: The experiments were conducted on male rats weighing 250g to 450g. Anesthesia was induced with 5% isoflurane in a gas mixture of O2/N2O (30%/70%) and maintained with 1.5% to 2.5% isoflurane during the entire surgical procedure. Catheters were placed in femoral veins and arteries on the left side of the animal respectively for tracer injection and manual blood sampling. On the right side, two beta-sensitive 250μm diameter microprobes were inserted respectively in the femoral artery (signal probe) and in the tissues just above the artery (to evaluate the background activity to be suppressed). In experiments where a probe was also placed in the striatum, the animal were mounted in a stereotaxic frame and a craniotomy was performed for the insertion of a microprobe (-0.5mm/Bregma, Lateral +3mm, Ventral –5mm from Dura Matter), a tracheotomy was also performed for mechanical ventilation. Physiological parameters (blood pO2; pCO2 and pH, body temperature) were monitored during the experiment.

Results and Conclusion: The method allowed to determine accurately the input function after bolus injection of 1mCi FDG (1ml over 60s) which was in good agreement with the input function simultaneously derived from blood sampling. The high temporal resolution (1s) avoided to miss the peak as sometimes observed with sampling. Since the ratio plasma to blood radioactivity versus time is very similar from one animal to another, it is possible to extract the plasma input function from the microprobes measurements. It was possible to determine accurate kinetics rate constants for the FDG model in the rat brain using three Microprobes simultaneously (two for the input function measurement and one for the FDG accumulation measurement in the brain). Finally, important technical improvements were brought by our study: (i) insertion of the probe in the femoral artery is quite simple and is comparable to the positioning of a catheter, (ii) use of a background suppression probe ensures an efficient background suppression provided it is well positioned above the artery. (iii) The sensitivity of the technique allows to monitor the input function even at late experimental times when the radioactivity concentration in blood has strongly decreased (iv) As the technique avoids blood collection, it should facilitate the quantitative modeling for radiotracers studies in small animals.

No. 53

[11C]LOPERAMIDE: A NOVEL AND HIGHLY SENSITIVE PET PROBE FOR QUANTIFICATION OF CHANGES IN P-GLYCOPROTEIN FUNCTIONALITY

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Introduction: P-glycoprotein, an ATP-driven transmembrane efflux pump, is known to play a major role in multidrug resistance leading to therapy failure in e.g. oncology and antiretroviral treatment and has recently been implicated in a number of conditions. Although a number of positron emission tomography (PET) probes have been described to measure changes in P-glycoprotein functionality, the difference between