# Small Animal PET/MRI: an *in vivo* Study in Oncology using a U87MG Mouse Glioma Model

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## INTRODUCTION

A PET insert based on LSO-APD detectors was built to be operated in a 7 T small animal MRI system (Fig. 1). The PET insert is based on avalanche photo diodes (APDs) being used as photo detectors in the high magnetic field of the 7T MRI System. A total of ten block detectors (12x12 LSO crystals 1.6x1.6x4.5mm³ per detector) are used to form a PET ring with 19 mm axial and 36 mm transaxial FOV. For MR imaging a quadrature body-resonator is used. Aim of this study was to investigate the potential of a combined PET/MRI system in the field of oncology. For this purpose an orthotropic model of U87MG glioma in nude mice in combination with a Carmustine based treatment was used. Imaging protocols were developed which take full advantage of this multimodality imaging combination.

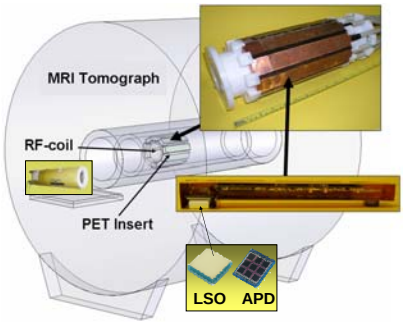


Figure 1: Developed PET/MRI System of Tübingen. The PET insert is composed of ten block detectors using a 12x12 LSO matrix which is read out with a 3x3 APD array. APD-PET signals are lead outside the 5 Gauss fringe line and processed to listmode data.

## MATERIAL AND METHODS

A group of eight nude mice were injected with U87MG cells after an initial irradiation. Cells were injected with a stereotactic fixation at the location of the right hemisphere of the brain. After 14 days mice developed small tumors of less than 1 µL volume and were randomized into two groups (treatment and vehicle). Tumor treatment using Carmustine (20mg/kg 3 times every 4 days) was given to the treatment group while the vehicle group received only the vehicle. PET/MR imaging was performed at day 14 (baseline) and 24 hours after each treatment day (Fig. 2).

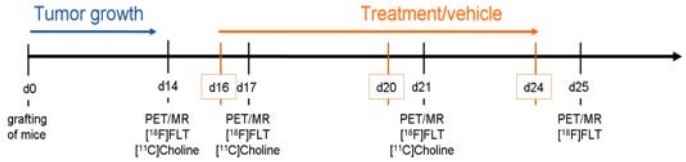


Figure 2: Study protocol. Mice were grafted with tumor cells at day 0. After 14 days of tumor growth animals were randomized in a treatment and vehicle group. PET MRI acquisitions were performed using [11C]Choline and [18F]FLT as PET tracers and T1, T2 weighted sequences, spectroscopy and contrast enhanced MR imaging.

PET/MR imaging was performed according to the protocol shown in Figure 3. Static PET data were acquired for 35 min using [11C]Choline (in the morning) and [18F]FLT (in the afternoon). Approximately 20 MBq of activity were injected and a 45 min unconscious uptake under 1.5% isoflurane anesthesia was allowed. Animals were positioned in the PET/MRI system during uptake of PET tracer and pre-contrast MRI imaging using T1 and T2 weighted sequences was performed. The PET acquisition was started 45 min post tracer injection. During PET measurements MR spectroscopy (MRS) and dynamic contrast enhanced imaging using Gadolinium based contrast agent injected via a tail vein catheter was performed.

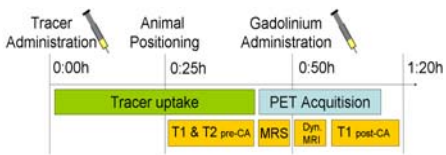


Figure 3: Schematic of the acquisition protocol

## RESULTS

The results of the combined PET/MRI acquisition at day 25 are shown in figure 4. The vehicle treated animals clearly show tumors in T2 weighted MR images and T1 weighted images post contrast agent administration. The [18F]FLT PET uptake matches well with the MR-images. The animal from the Carmustine treated group shows only faint uptake of the [18F]FLT and has a much smaller sized tumor which is much better visualized after contrast agent administration. The treated tumor lesions are difficult to delineate from the non-specific PET tracer uptake. In this case the MR image with high soft tissue contrast is of high value for accurate PET tracer uptake quantification.

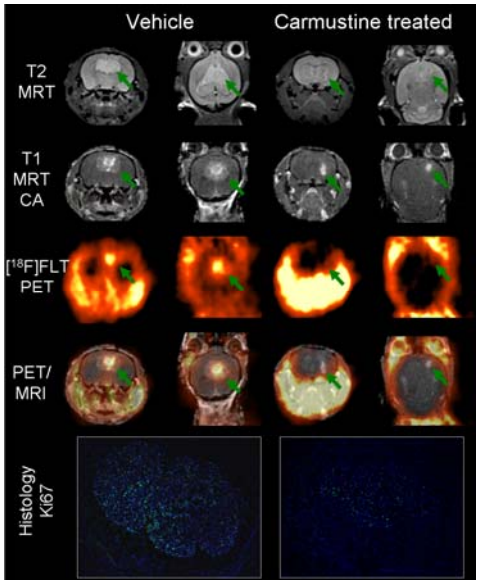


Figure 4: Results of combined PET/MRI acquisitions using [18F]FLT. Images of a vehicle and Carmustine treated animal at day 25 are displayed. Tumors are to be visualized well in MR images with and without contrast agent. PET images of the treated animal show reduced [18F]FLT tracer uptake. The [18F]FLT uptake shows good correlation with Ki67 fluorescence stain.

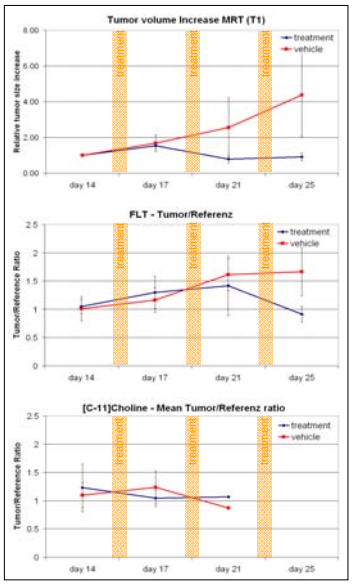


Figure 5: Volumetric tumor measurements were done based on the MRI data (top). Tumor growth shows significant reduction in MRI already after first treatment. PET data of [18F]FLT appear to respond delayed to treatment. [11C]choline shows no significant reduction in uptake.

## CONCLUSION

Based on MR images tumor regions of interest (ROI) were delineated and volumetric measurements were performed. As tumor sizes were very heterogeneous, they have been normalized to initial size (day 14). MRI based tumor growth curves are shown in Fig. 5 (top). Therapeutic effects can be seen due to reduced growth in treated animals.
Since PET images are accurately registered due to the combined PET/MRI system, ROIs from the MR data were transferred to PET images. A reference ROI was placed in the left hemisphere to generate tumor/reference ratios uptake values. [18F]FLT showed a significant effect of the Carmustine treatment due to reduced tumor to reference ratios. However, response in [18F]FLT appears to be delayed compared to reduced tumor growth effects. [11C]Choline data did not detect early treatment effect in this tumor model. Histological preparation of Carmustine and vehicle treated tumor section using Ki67 fluorescence staining showed increased proliferation in untreated tumors versus treated tumors (Fig. 4, bottom). Further studies will follow including [11C]Methionine PET scans and immunohistochemistry of Ki67 and tk1.

**For these studies, combined PET/MR brought the following advantages compared to sequential PET and MR imaging:**

1. **Reduction of scan and anesthesia time by almost a factor of two**
2. **Accurate co-registration and quantification of PET images based on MR morphology**
3. **Complimentary information generated from PET and MRI about treatment response and efficacy as well as cell proliferation.**