[^{18}F]FDG and [^{18}F]FLT PET imaging in orthotopic mouse brain tumor model

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1. Introduction

Fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) is widely used in cancer research such as staging, monitoring therapeutic response and the follow-up [1]. FDG is taken by glucose transporters, phosphorylated and then trapped in the cell.

3'-[^{18}F]fluoro-3'-deoxythymidine ([^{18}F]-FLT) has been developed for cell proliferation imaging by PET. It has been used to monitor tumor uptake in models. It is transported into the cytosol, where it is phosphorylated by thymidine kinase 1 (TK1). Phosphorylated [^{18}F]FLT is trapped in the cell [2].

FDG is valuable, but not in all tumors, especially brain tumor. [^{18}F]FDG exhibits highly uptake in the normal brain, but [^{18}F[FLT shows low uptake in normal brain. Due to these properties, the usefulness of [^{18}F]FLT has been demonstrated in preclinical and clinical studies [3,4]. However, comparison between [^{18}F]FDG PET and [^{18}F]FLT PET was not reported in orthotopic brain tumor model of mice.

The purpose of this study was to compare PET imaging with [^{18}F]FDG and [^{18}F]FLT and evaluate the feasibility for monitoring the brain tumor progression in mouse orthotopic xenograft model.

2. Methods and Results

2.1 [^{18}F]FDG and [^{18}F]FLT systhesis

[^{18}F]FDG was obtained from fully automated FDG MX module (GE Healthcare). [^{18}F]FLT was synthesized according to reported method [5] with radiochemical yield of 20–30%. The specific activity of [^{18}F]FDG and [^{18}F]FLT were > 37 GBq/μmol and radiochemical purity of those were > 98%.

2.2 Orthotopic brain tumor model

BALB/c nude mice (female, 6 weeks old, n = 6) were used in all experiments. To establish the intracranial U87MG xenografts, 1×10^5 cells in 6 μL of PBS were injected through the skull of anesthetized mice (Ketamine/ Rompun mixture) in the right frontal lobe at 2 mm lateral, 0.5 mm anterior from the bregma and a depth of 3 mm from dura using a Hamilton syringe with a 27-gauge needle. After implantation, the burr hole was covered with dental cement and the skin was sutured.

2.3 Magnetic resonance imaging

Animals were anesthetized using 2% isofluorane. Mice were placed in the wrist coil. MR imaging was performed on a 3T clinical MRI instrument (Siemens). T2-weighted images were acquired at 8, 15 and 22 days after tumor cells injection. T2-weighted axial images (TE= 53 ms; TR = 2,700 ms; flip angle = 120; field of view = 25 mm^2; matrix size = 256 x 128; slice thickness = 0.8 mm) were acquired. T2-weighted coronal images (TE= 51 ms; TR = 3,000 ms; flip angle = 120; field of view = 60 mm^2; matrix size = 192 x 192; slice thickness = 0.8 mm) were acquired.

2.4 Small animal PET/CT imaging

[^{18}F]FDG and [^{18}F]

FLT PET/CT imaging were performed with same mice before or after T2-weighted MR imaging. [^{18}F]FDG (7.4 MBq, 200 μCi) was injected via tail vein 1 h prior to PET/CT scanning. [^{18}F]FLT (same dose) was injected 2 h prior. Mice were anesthetized using 2% isofluorane. PET and CT images were acquired using small animal PET/CT scanner (INVEON, Siemens). After CT acquisition, mouse was moved to the PET scanner on the same bed and scanned for 20 m. CT images were reconstructed using the COBRA software (Exxim). The reconstruction pixel size was 0.22 x 0.22 x 0.22 mm on a 256 x 256 x 256 image matrix. PET images were reconstructed using OSEM2D algorithm. The reconstructed pixel size was 0.078 x 0.078 x 0.078 on a 128 x 128 x 159 image matrix.

PET images were represented as %ID/g (Fig. 2). Small animal PET/CT and PET images were analyzed by Inveon Research Workplace (Siemens).

2.5 Image analysis

Tumor growth was identified in MR images (Fig. 1). As times goes by, tumor size was expanded in both axial and coronal images. Tumor volume was 1.6 ㎜^{3}, 12.0 ㎜^{3} and 17.3 ㎜^{3} at 8, 15 and 22 days, respectively, in represented MR images.

[^{18}F]FDG uptake of tumor and normal brain was 9.5 ± 0.9 and 9.7 ± 1.0 %ID/g, respectively, at 21 days and tumor-to-normal brain (T/N) ratio was 0.97. There was not different [^{18}F]FDG uptake between tumor and normal brain (P = 0.75). [^{18}F]FLT uptake of tumor and normal brain was 11.9 ± 2.2 and 0.3 ± 0.03 %ID/g, respectively, at 22 days and T/N ratio was 45.6.

[^{18}F]FLT tumor uptake was significantly high compared to normal brain uptake (P < 0.001). There was statistically no difference (P = 0.18) in tumor uptake between [^{18}F]FDG and [^{18}F]FLT.

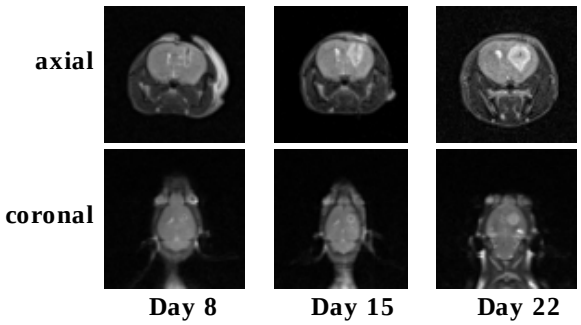

Fig. 1. T2-weighted axial and coronal MR images in same mouse at 8, 15 and 22 day after tumor injection.

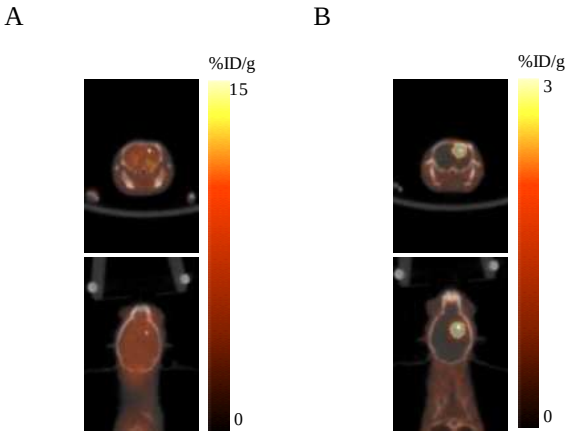

Fig. 2 Small animal PET/CT images. A, [^{18}F]FDG PET/CT images. B, [^{18}F] FLT PET/CT and PET images.

3. Conclusions

In this study, intracranial gliomas bearing mouse model was used to investigate the suitability of [^{18}F]FLT PET to monitor tumor growth in mouse brain. [^{18}F]FLT was well accumulated in brain tumor and tumor region was delineated from normal brain. In contrast, due to physiologically high uptake of [^{18}F]FDG in the brain, it was not feasible to distinguish the tumor region from the brain.

[^{18}F]FLT PET may provide the usefulness for monitoring brain tumor growth and therapeutic response by various therapeutic regimens in orthotopic brain tumor model

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